A ‘hair-raising’ history of alopecia areata

David Broadley[1], Kevin J McElwee[1,2,*]

1. Centre for Skin Sciences, University of Bradford, Bradford, West Yorkshire, United Kingdom
2. Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

Link to published article: www.doi.org/10.1111/exd.14073

*Corresponding author: Kevin McElwee. Centre for Skin Sciences, University of Bradford, Bradford, West Yorkshire, BD7 1DP, UK.

Funding source: Alopecia UK

Conflicts of Interest: Kevin McElwee is Chief Scientific Officer for Replicel Life Sciences Inc.

Abstract word count: 249

Word count for the text: 4432

The number of references: 240

The number of figures: 4

The number of tables: 2

Key Words: Alopecia areata; history; pathogenesis; treatment;

Author contributions: DB and KM reviewed the literature, compiled the reference list, and wrote the article.

Abstract

A 3500 year old papyrus from ancient Egypt provides a list of treatments for many diseases including “bite hair loss”; most likely alopecia areata (AA). The treatment of AA remained largely unchanged for over 1500 years. In 30 CE, Celsus described AA presenting as scalp alopecia in spots or the “windings of a snake”, and suggested treatment with caustic compounds and scarification. The first “modern” description of AA came in 1813, though treatment still largely employed caustic agents. From the mid-19th Century onwards, various hypotheses of AA development were put forward including; infectious microbes (1843), nerve defects (1858), physical trauma and psychological stress (1881), focal inflammation (1891), diseased teeth (1902), toxins (1912), and endocrine disorders (1913). The 1950s brought new treatment developments with the first use of corticosteroid compounds (1952), and the first suggestion that AA was an autoimmune disease (1958). Research progressively shifted towards identifying hair follicle specific autoantibodies (1995). The potential role of lymphocytes in AA was made implicit with immunohistological studies (1980s). However, studies confirming their functional role were not published until the development of rodent models (1990s). Genetic studies, particularly genome wide association studies, have now come to the forefront and open up a new era of AA investigation (2000s). Today, AA research is actively focused on genetics, the microbiome, dietary modulators, the role of atopy, immune cell types in AA pathogenesis, primary antigenic targets, mechanisms by which immune cells influence hair growth, and of course the development of new treatments based on these discoveries.

Introduction

The history of alopecia areata (AA) is at least 3500 years old (Table I). However, researchers active in AA investigation have seen the field advance most significantly over the last ~30 years. From an average of 15 publications on AA per year in the 1950s, ~25 per year in the 1970s, ~55 in the 1990s, to ~170 per year in the 2010s, the annual count is still small, but growing exponentially (Fig 1a). Only having to read around 50 new AA publications each year made life easy as a naïve PhD student in the 1990s (KM), but also daunting in that so little was understood about the nature of the disease. Nevertheless, the knowledge to draw on was rather better than for the first collegiate scholars of AA who presented brief dissertations to the Universities of Frankfurt and Berlin in 1857 and 1862.[1,2] A modern student of AA has rather more publications to contend with (DB), but also a relatively better framework of understanding. This review provides a summary of the progress we have made in AA over the last few millennia.

Early history

It has been suggested that AA is described in the ancient Vedas (5000-400 BCE) of Ayurvedic medicine,[3] though it is difficult to confirm the chronological provenance. The first known historical record of AA that can be claimed with reasonable confidence is written in the "Ebers papyrus". Found between the feet of an Egyptian mummy and believed to date to 1500 BCE,[4] the papyrus is the most extensive record of ancient Egyptian medicine yet discovered. It is primarily a list of medical treatments for use in the afterlife (Fig 2). In different locations, there are brief listings for "Nssq" hair loss which is believed to refer to patchy AA.[5,6]

The 35th chapter of Hippocrates' book "*On Diseases*" (~400 BCE) fleetingly alludes to blemishes where the hair is "foxy" in areas (after the Greek αλώπηξ = alopex, fox's disease, alopecia), probably referencing mange which is relatively common in foxes.[7] While it is not entirely clear whether Hippocrates was describing AA or androgenetic alopecia, mange can present in distinct patches visually similar to AA. AA may also have been described in ancient Chinese texts, though again it is not clear. Emperor Huang Ti (2696-2595 BCE), is credited for

writing twelve scrolls which were eventually compiled (between 300-400 BCE) into a medical text now known as: "*the Yellow Emperor's Classic of Internal Medicine*". The text suggests that scalp or body hair can fall out if dietary food is too pungent, too bitter, or too sweet.[8]

The first fully recognizable descriptions of AA are attributed to Cornelius Celsus (25 BCE - 50 CE), a Roman encyclopedist translator of medical work. Celsus was not himself a doctor and most likely his translations were derived from the works of Menekrates (359-336 BCE). In the 4th chapter of his 6th book *De Medicina* (~30 CE), Celsus described "*Alopekia*", bald spots (after the Greek αλωπεκία = alopecia) which occurred in both the scalp and the beard; and "*Ophiasis*", bald areas that spread like the windings of a snake (after the Greek φίδι = snake). The ophiasis Celsus characterizes is not entirely the same as ophiasis AA defined today. Rather, Celsus describes ophiasis AA commencing at the back of the scalp, and "without exceeding two fingers in breadth" extends itself by two points of prolongation towards the ears, and in some it progresses onto the forehead, until the "two heads unite".[9,10]

Italian physician Girolamo Mercuriale (1530-1606), wrote "*De morbis cutaneis*" in 1572; generally considered the first "modern" scientific tract on skin diseases. AA is discussed within the book very much as a reflection of the ancient Greek transcripts, with respect to AA and treatments for the condition (see below).[11] There was very little change in the presentation and advice on AA treatment in medical texts for ~1500 years. The works of Hippocrates, Celsus, and Galen, as well as the interpretations of Persian scholars, were frequently cited in transcripts until the 18th Century (eg.[12-14]).

The first "modern" description of AA is widely attributed to Thomas Bateman (1778-1821) and Robert Willan (1757-1812). Instead of classifying skin diseases based on symptoms, Willan developed a system based on the appearance of skin disorders. After his death, Bateman continued to develop the system and published "*A Practical Synopsis of Cutaneous Diseases According to the Arrangement of Dr Willan*" in 1813. Bateman describes the essential characteristics of AA in patches, and cites Celsus. He alludes to infectious AA in groups of children, but also defines AA that occurs in isolation.[15]

Possibly the first visual description of AA is in the painting of "Saint Sebastian" (1480; Paris, Louvre) by Andrea Mantegna. The bowman in the painting may have alopecia barbae.[16] The first dermatology atlas to show AA was published in 1817 entitled "*the Delineations of Cutaneous Disease*".[17] It contains an engraved, hand colored plate of a male with multiple patches of AA (Fig 3). The first photographic image of AA was published in 1868 in a clinical atlas of dermatology showing a young boy with extensive AA.[18]

What's in a name?

AA has been given many different names throughout history.[19] The first known term for AA written in the Ebers papyrus translates as bitten or "*bite alopecia*";[5,6] a reasonable description of patchy AA. As is often cited, the word "*alopecia*" was used by Hippocrates,[20] while "areas" of alopecia were first described by Celsus.[9] In early literature, AA was sometimes known as "*area Celsi*" or "*alopecia Celsi*" as an acknowledgement.[21-24] Also possibly in reference to Celsus' description, AA was occasionally referred to in early texts by colloquial names including "*fox's-evil*".[25] In medieval and renaissance texts, AA is often referred to simply as "*alopecia*", though the word can be written in different ways including "*allopitie*",[12] "*allopicia*",[13] *alopecy*",[26] and "*alopefia*",[14] among other variants.

A description of an alopecia patch was first provided by the German physician Johannes Jonston (1603-1675) in his book "*Medicina Practica*" (1664).[27] He wrote on the "alopecia area": "*Area est capillorum area-tim defluvium*". Consequently, rather than using the name Jonston provided, AA was sometimes known as "*Area Jonstoni*" (Jonston's alopecia). The phrase "*alopecia areata*" was first used by the French dermatologist François Boissier Sauvages de Lacroix in his book "*Nosologia Methodica*",[28] However, while the term was first published in 1763, it took some considerable time for AA to become the near universally accepted description that is used today.

In the 19th Century, "*porrigo decalvans*" was the more common term used for AA. Often first attributed to Willan,[29] the term comes from classical Latin; porrīgō, meaning scurf, or dandruff,

and dēcalvāns, meaning baldness. As the name suggests, there was considerable confusion between AA and ringworm, a confusion that persisted into the 20th Century. Due to this conflation, at times AA was also labelled as "*tinea decalvans*".[30,31] Based on the claim that AA was due to an infectious agent, Gruby suggested the name "*phytoalopecia*".[32] Wilson first described AA as "*accidental alopecia*".[33] Later, he used the term "*porrigo decalvans*",[34] but "*accidental alopecia*" and "*alopecia accidentalis*" were used in several 19th Century publications. While the approach is not perfect,[35], using "Google Ngrams viewer",[36] one can see use of the term "*porrigo decalvans*" declined, while "*alopecia areata*" gradually gained acceptance from the 1850s onwards (Fig 1b).

Names for variants and subtypes of AA can also be found. "*Cazenave's vitiligo*", "*Celsus' vitiligo*", "*vitiligo capitis*", and "*achromatous porrigo*" were terms used to describe vitiligo of the scalp in association with AA.[37-39] Cazenave (1795-1877) suggested AA was a subtype of vitiligo and made a connection between inflammation, vitiligo and AA.[40] He also indicated changes in hair color and blanching could occur and, along with Rayer, that hair regrowth in AA patches tends to be initially non-pigmented.[41,42] In parallel, Bazin named AA with hair depigmentation "*tinea achromasota*".[43,44] Over time, "*Cazenave's vitiligo*" was more loosely applied to describe white hair in AA.

The term "*alopecia ophiasis*", clearly derives from the original descriptions by Celsus. The first time in print for the term "*alopecia barbae*" is in a German-Latin dictionary from 1691.[45] However, it takes 175 years before it appears again.[46] The term "*alopecia circumscripta*" was a term probably first used by Fuchs and logically describes the patchy nature of AA.[39] The term "*alopecia universalis*" first appeared in publications from 1739,[47] "*alopecia totalis*" from 1839,[48] and "*patchy alopecia areata*" as a specific definition appeared in 1895 (Fig 1c).[49] Identification of diffuse AA "*Alopecia areata diffusa*" did not occur until the mid-20th Century.[50]

Of course the above nomenclature is primarily English vernacular derived from Latin and Greek. In other countries, languages, and systems of medicine, AA was, and still is, sometimes identified by other names. In French medical literature "*La Pelade*" was a common term used until quite recently. More rarely, "*teigne pelade*" "*pelade achromateuse*", "*pelade ophiasique*"

and "*pelade décalvante*" were used.[7] For India, in Ayurveda principles of medicine, AA is called "*Indralupta*" and "*Ruhya*" for alopecia universalis.[51] In early Chinese texts AA received various names including "*ghost shaved hair*", a colloquial term that is sometimes still used.[52] In Chinese traditional medicine today, AA is usually defined as "*oily wind*", a name that can be traced back to 1617 and Chen Shigong's book "*Surgical Authentic*".[53]

Treatments for AA

The Ebers papyrus advocates several treatments (Fig 2) including a fig, sebesten, yellow ochre, frankinsense, goose-fat, and sweet beer mixture, applied to the scalp.[5,6] Various treatments were suggested by the ancient Egyptians, with two purportedly from Queen Cleopatra herself.[25,54-56] Ancient Greek physicians recommended a plethora of therapeutic approaches using chemicals, herbs, and physical interventions (Table II). Celsus specified scarifying bald patches with a scalpel; and that; "some are painting on caustics mixed with oil, and especially burnt papyrus; some turpentine-resin with fennel".[9] Pliny the elder (23–79 CE) suggested onion mixed with honey or vinegar for AA. Persian scholar Rhazes (865–925 CE) cites Antyllus (~150 CE) as recommending scarification, cupping, and leeches.

In the Middle Ages AA was believed to be due to corruption of the blood by black bile. Consequently treatment focused on improving the blood in various ways. In 1127, Stephen of Antioch produced a Latin translation of "*Liber regalis*" (al-Kitab al-Maliki) the work of Persian physician Hali Abbas (982–994 CE). In the "*Practica*" the text recommends bloodletting, pills and purges for AA.[12] During the Renaissance, physicians significantly expanded treatment options, often with a focus on herbal remedies (Table II). By the early 18th Century, Turner (1667–1741) variously recommended; rubbing with a coarse linen cloth, fig-leaves, and onions to make the skin "wax red", leeches, scarification, or acupuncture, followed by labdanum resin, pigeons-dung, delphinium plant seeds, bay leaf oil, turpentine and wax. Indeed, anything "which may excite or stir up the heat" and attract "nourishment to the parts".[57]

In the 19th Century, later editions of Bateman's book "*on skin diseases*" suggested treatment by shaving, using friction, and oil of Mace dissolved in alcohol or prepared with tar oil, bitumen,

camphor, or turpentine.[58] Wilson recommended cantharides and lavender oil,[33] or iodine and antimony.[16] Fox endorsed mercury ointment.[31] By the early 20th Century, a wide range of treatments were used for AA and there was little consensus on what was effective.[59-61] In France, where the view lingered that infectious agents caused AA, antiseptic treatments continued to be promoted (Fig 4a).

Reviewing the therapeutic modalities through history, it is notable that from the ancient Egyptians onwards, often the primary objective was to encourage skin irritation using physical or chemical methods. Irritant treatments, such as dinitrochlorobenzene and anthralin,[62,63] and contact sensitization treatments such as squaric acid and diphencyprone,[64,65] are effective AA therapies still in use today. In contrast, the 1950s brought a significant change in direction towards immuno-suppressive agents. In 1952, Dillaha and Rothman first used cortisone acetate to treat AA.[66,67] They were, however, unclear on the mode of action, attributing the effect to "a change in local chemical milieu through some such manner as influencing sebaceous gland function or keratinization". Later, it was recognized that corticosteroids act on inflammatory cells.[68] While there have been attempts to develop other immuno-suppressive agents for AA (eg.[69,70]), corticosteroids remain the first treatment approach in most clinics worldwide. New immuno-regulatory treatments, such as JAK inhibitors, are on the horizon;[71] time will tell if they become a mainstream therapeutic approach.[72]

Hypotheses for AA pathogenesis

The first attempt to explain AA pathogenesis comes from Chao Yuanfang (581–618 CE), a Chinese physician of the Sui Dynasty era. In his text "*Treatise on the Origin and Symptoms of Diseases*", for AA pathogenesis he states; "There are people who have been invaded by the evil wind spirits in their heads. If they have a deficiency, they will lose their hair, their muscles will die. The hair loss patch can be just as big as a coin, or like a finger (in shape). The hair loss is long-lasting and not itchy, so it is called a ghost's lick".[73] Later in the Ming dynasty, Chen Shigong (1555–1636), in his text "*Surgical Authentic*" states that AA; "is a blood asthenia (lack of energy) and cannot support the skin with qi (vital energy) and nourish the skin, so the hair

roots are empty and peel off into pieces. The skin will be smooth and shining, itchy like insects crowing. It is because of the Hot Wind attack when the body is more on the asthenia side".[53] With the onset of modern medicine in the 19th Century, efforts were made to research the underlying causes of AA.

AA caused by infectious agents

Gruby first presented an infectious agent hypothesis to explain AA pathogenesis in 1843.[32] He discovered a fungus "*Microsporum audouini*" around the hairs in his *Porrigo decalvans* patients. The parasitic hypothesis for AA superficially made sense; the hair loss lesion expanded in size as a local infection would. The characteristics of AA, displaying rapid hair loss in a patchy manner, was similar to that seen in patients with ringworm or syphilis. A secondary effect of AA is that it can affect nail development, also similar to observations for syphilis.[60,61] Reports of AA "epidemics" in institutions such as schools and orphanages were reported,[15,74-77] which further circumstantially supported a parasitic hypothesis. The infectious agent explanation of AA pathogenesis became widely accepted at the time and the idea that AA was contagious persisted into the 20th Century. In France, development of AA was a cause for exemption from military service (Fig 4b).[78]

However, data gradually accumulated against an infectious agent hypothesis.[79] Some dermatologists isolated different fungi.[80,81] Thin identified bacteria associated with AA and promptly renamed the condition "*bacterium decalvans*".[82] Bazin and Stowers viewed AA as caused by "*tinea tonsurans*" infection.[43,83] Other dermatologists failed to identify any infectious agents unique to AA,[84] and attempts to transfer the disease by inoculation also failed.[85] Inevitably, the most likely explanation for Gruby's observation was the ambiguity in diagnosis between AA and tinea capitis at the time. Indeed, Sabouraud later concluded that Gruby was in fact studying patients with ringworm.[27,86] Gradually, dermatologists shifted their opinion against an infectious cause of AA.[87,88]

Although the idea that an infectious agent directly causes AA has been laid to rest, there is still a possible role for pathogen superantigens in increasing the general activity of the immune system, or more specifically by activating AA via antigen epitope mimicking.[89,90]

AA as an atrophic nerve disorder

Due to the inability to convincingly identify an organism with an etiological relation to AA, the idea of nerves being involved in AA was put forward relatively early and rapidly gained followers. Cazenave appreciated the frequent association of AA and vitiligo which he believed to be of nervous origin.[91] With a detailed investigation, von Bärensprung showed nerve atrophy in AA affected skin and associated this with trophic nerve paralysis.[24] Supporters of the AA "trophoneurosis theory" (also called the trophoneurotic, neurotrophic, or neuropathic theory) claimed other evidence supported this, such as apparent changes in skin sensation in the affected areas and neuralgic symptoms appearing before or during AA onset.[79] Collier reported a case of a boy who was struck over the left ear in a fight, causing intense neuralgia, followed by AA of the left parietal region.[10] A string of reports and studies followed linking changes to nerves with AA development (eg.[92]).

More direct evidence was put forward by Max Joseph. Joseph showed that focal alopecia could be induced by cutting the spinal ganglia of the second cervical nerve in the necks of cats. After several days, he observed patchy hair loss develop in the region of skin that the nerve supplied. When he examined the skin's histology he identified hair follicle atrophy, while the sweat and sebaceous glands were unaffected.[93,94] These studies were not universally accepted however,[95] and Aubrun concluded that the alopecia was merely a consequence of scratching.[96] A more intriguing variation on the neuropathic theory was put forward by Jacquet. He suggested AA was initiated by nerve irritation caused by defective and diseased teeth.[97] Jacquet's claim was apparently confirmed by others.[98,99] AA was also suggested to be linked to eye strain.[100,101]

In more recent times, it has been shown that there are changes in the structure and signaling systems of nerves in areas of AA.[102,103] Increased cutaneous stimulation may indeed be needed

for sensory perception in AA skin.[104] While nerve atrophy has been discounted as a primary cause of AA, there may be links between AA lesions and nerve innervation in affected skin and possibly other tissues.[105]

AA as a psychosomatic disorder

Over time the primarily physiological, neuropathic theory of AA pathogenesis transformed into a predominantly psychosomatic theory. This idea was supported by the frequent clinical observations of emotional stress and psychological trauma in advance of AA onset. Kinney presented a case of AA a few days after a shock caused by lightning striking a tree near the patient.[106] Subsequently, similar examples were reported in medical journals (eg.[100]). For the most part the publications were case reports, there were few attempts to analyze large patient cohorts until the 1950s. A well cited study from Sheffield reported that AA was preceded by mental stress in 23% of 114 cases.[107] Several reviews and investigations were then published linking psychosomatic issues to AA.[108-110] The stress theory of AA eventually gained the support of many dermatologists at the time. Of course the role of stress in AA continues to be actively investigated (eg.[111]).

AA induced by toxins

In the early 20th Century, another hypothesis of AA induction was put forward based on toxins inducing hair loss.[112] The sudden remission and relapse of AA and its action in multiple regions of skin simultaneously over the scalp and body circumstantially supported the idea.[113] Additionally, injection of thallium acetate was shown to induce AA-like hair loss.[112,114,115] AA was reported resulting from injections of quinine dihydrochloride and urethane,[116] or after exposure to ethyl gasoline.[117] Toxin induced AA was believed to stem in part from nerve atrophy due to the toxin effects and/or atrophy of the parathyroid glands.[118] The toxic theory of AA pathogenesis never gained widespread popularity. Of note however, isolated reports still suggest a possible link between chemical exposure and AA onset (eg.[119]).

AA as an endocrine disorder

With the start of the 20th Century AA was known to be associated with endocrine disorders, particularly of the thyroid. Sabouraud presented cases of AA in association with goiters,[120] while others suggested AA improved after treatment for hypo- and hyperthyroidism.[121,122] Sabouraud also reported changes in AA during pregnancy and menopause.[123,124] Analysis of 230 AA patients by Walker and Rothman revealed examples of thyrotoxicosis and hair regrowth during pregnancy.[125] However, despite these reports, the hypothesis that AA was due to an endocrine disorder gained relatively little traction. The increased risk for development of autoimmune thyroid disorders in AA patients is now well recognized,[126] but the mechanism of association remains unclear.

AA as an inflammatory disorder

The earliest mention of inflammation in relation to AA in "modern" medical literature came from Wilson (1840) who very briefly suggested that the local cause of AA was defective nutrition due to poor capillary supply, or inflammation.[33] The first evidence for inflammatory cells in and around hair follicles was produced from a post-mortem histological analysis of scalp skin.[127] Surprisingly, despite observing leucocytes, and publishing the first drawing of hair follicle histology with inflammation, the authors dismissed their remark and focused on nerve atrophy. Later, Robinson observed peri-vascular and peri-follicular "round cell" infiltration by histology, but did not attempt to explain it.[79] Unna, while concluding that AA was due to an infectious agent, also described inflammation in AA.[128]

In 1891, Italian dermatologist Sébastien Giovannini examined 20 cases of AA using serial histological cross sections to reconstruct AA affected skin.[129] His publication paints a picture of AA that would be recognized today. The progressive focal inflammation of anagen hair follicles, invasion of the dermal papilla, hair bulb matrix and root sheaths, disruption of hair follicle

integrity and cell apoptosis, the regression of hair follicles into catagen, and the subsequent loss of hair, are well described. He claimed that inflammation could be observed in areas of skin in advance of hair loss and that there is infiltration of leucocytes into the follicles in all cases. Most significantly, Giovanini drew the bold conclusion that AA was directly caused by inflammation.

However, Giovannini's work failed to generate much interest. Unna acknowledged the "valuable" work of Giovannini, but disputed his conclusions on the significance of inflammation. His rejection seems to be based on his own observations that "markedly atrophic follicles, with almost no cellular infiltration around the deep part of the follicle" can be found in AA.[128] Only much later, studies essentially confirmed Giovannini's work and renewed interest in the local immune cell infiltrate.[130-133]

AA as an autoimmune disorder

Little progress was made in understanding AA pathogenesis until the late 1950s. Stephen Rothman was the first (known) person who referred to the possibility of autoimmunity in AA during the discussion of a presentation made in 1958.[134] Rothman speculated that AA may be; "due to a displacement of melanin from melanocytes and to a subsequent allergic reaction with the formation of antimelanin antibodies. If this is so, cortisone and its derivatives may act as anti-allergic and anti-inflammatory agents". This observation slowly gained momentum and it took some time before AA research refocused on autoimmunity.

Attempts were made to identify autoantibodies in AA patients, though initially with little success.[135-137] Later, however, studies confirmed the presence of autoantibodies to various tissues in AA patients. Anti-nuclear antibodies,[138,139] thyroid autoantibodies,[140-142] antibodies against smooth muscle,[143] and gastric parietal cells were all found.[141] Endeavors to detect autoantibodies against hair follicle antigens initially failed.[144-146] Eventually, reports were published demonstrating hair follicle specific autoantibodies present in AA affected patients and animals with AA.[147-150] This was a significant step in that the studies were the first to confirm the immune system could mount a specific autoimmune response against hair follicle antigens.[151]

The realization of a role for T lymphocytes in AA

While the initial focus of autoimmune research in AA was on autoantibodies, it soon became apparent that a T cell mediated mechanism of AA pathogenesis was more likely. Little or no consistency in the targets for AA autoantibodies could be identified. Further, injection of AA patient serum into human scalp skin grafts on nude mice had no impact on hair growth.[152] As the importance of autoantibodies in AA pathogenesis seemed to be limited, the focus of research (re)turned towards cellular inflammation. However, autoantibodies may yet have a significant role to play in directing research towards particular antigen epitopes.[153,154]

It was suggested that hair follicles may have "immune privilege" and that its breakdown leads to AA.[155,156] Paus and colleagues presented a hypothesis of AA pathogenesis based on autoreactive $CD8^+$ cells targeting and disrupting hair follicles.[157] They suggested microtrauma induced a localized "immune privilege collapse" in hair follicles which elicited a cytotoxic lymphocyte attack.[158] While the proposal largely ignored conventional explanations for cell mediated autoimmune disease development (and still does), the hypothesis gained traction. Independently, McDonagh and Messenger also outlined a scenario in which hair follicles are attacked by lymphocytes [159]. Consequently, there was considerable debate as to the role of lymphocytes in AA at the first few workshops on AA, organized by the National Alopecia Areata Foundation.[160]

Animal models for alopecia areata

As momentum began to build behind the idea that T cells could drive AA, new research tools were being developed; namely, rodent models of AA. Gilhar and colleagues began to manipulate AA skin grafted to nude mice, and later SCID mice, to show hair regrowth was possible in the absence of inflammation,[161,162] to show autoantibodies were not pathogenic,[152] to investigate the role of interferon-γ in AA,[163] and ultimately to show that melanogenesis related peptide stimulated lymphocytes could induce AA in scalp skin.[164,165] This was the first functional

evidence that AA could be induced by transferring T cells into scalp skin and that hair follicle autoantigens could be involved in activating inflammatory cells.

In the early 1990s, two models exhibiting spontaneous AA development were characterized; the "Dundee Experimental Bald Rat" (DEBR)[166,167] and the C3H/HeJ mouse.[168] With the DEBR model, antibodies were used to deplete $CD8^+$ cells,[169] and later $CD4^+$ cells,[170] to show that hair regrowth was possible with the removal of either cell population. The rat model was also used to investigate treatments for AA.[171-173] Unfortunately, due to poor fecundity the DEBR colony died out in 2015, but the model served its purpose and provided evidence in support of a cell mediated AA disease mechanism.

After developing the spontaneous C3H/HeJ mouse model into a skin graft induced model,[174] a series of studies were conducted looking at immune cell infiltration in advance of hair loss,[175] examining treatments and modes of action,[176,177] demonstrating that blockade of skin homing T cells using antibodies enabled hair regrowth,[178] and beginning some, albeit limited, studies to investigate factors that may modulate susceptibility to AA.[179-181] Over the past ~30 years, rodent models have gradually, if rather fitfully, become accepted as a useful tool with which to investigate AA.[182]

Alopecia areata research in the modern age

As we enter the next millennia, genetic studies, particularly genome wide association studies, have now come to the forefront and open up a new era of investigation.[183] Our understanding of AA pathogenesis has advanced significantly, though it still has many gaps. Today, AA research is active in genetics,[184,185] the microbiome, the role of the environment, the role of atopy,[186] immune cell types in AA pathogenesis,[187] primary antigenic targets,[153] mechanisms by which immune cells influence hair follicles, and of course the development of new treatments based on these discoveries. This increased AA research activity (Fig 1), from a larger number of professionals, promises momentous developments to come!

Acknowledgements

We would like to thank Prof. Xingqi Zhang for information and translation of Chinese texts. Our thanks to Dr. Eddy H-C Wang for assistance with figures. Thanks to Alopecia UK and the National Alopecia Areata Foundation for their support.

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Figures

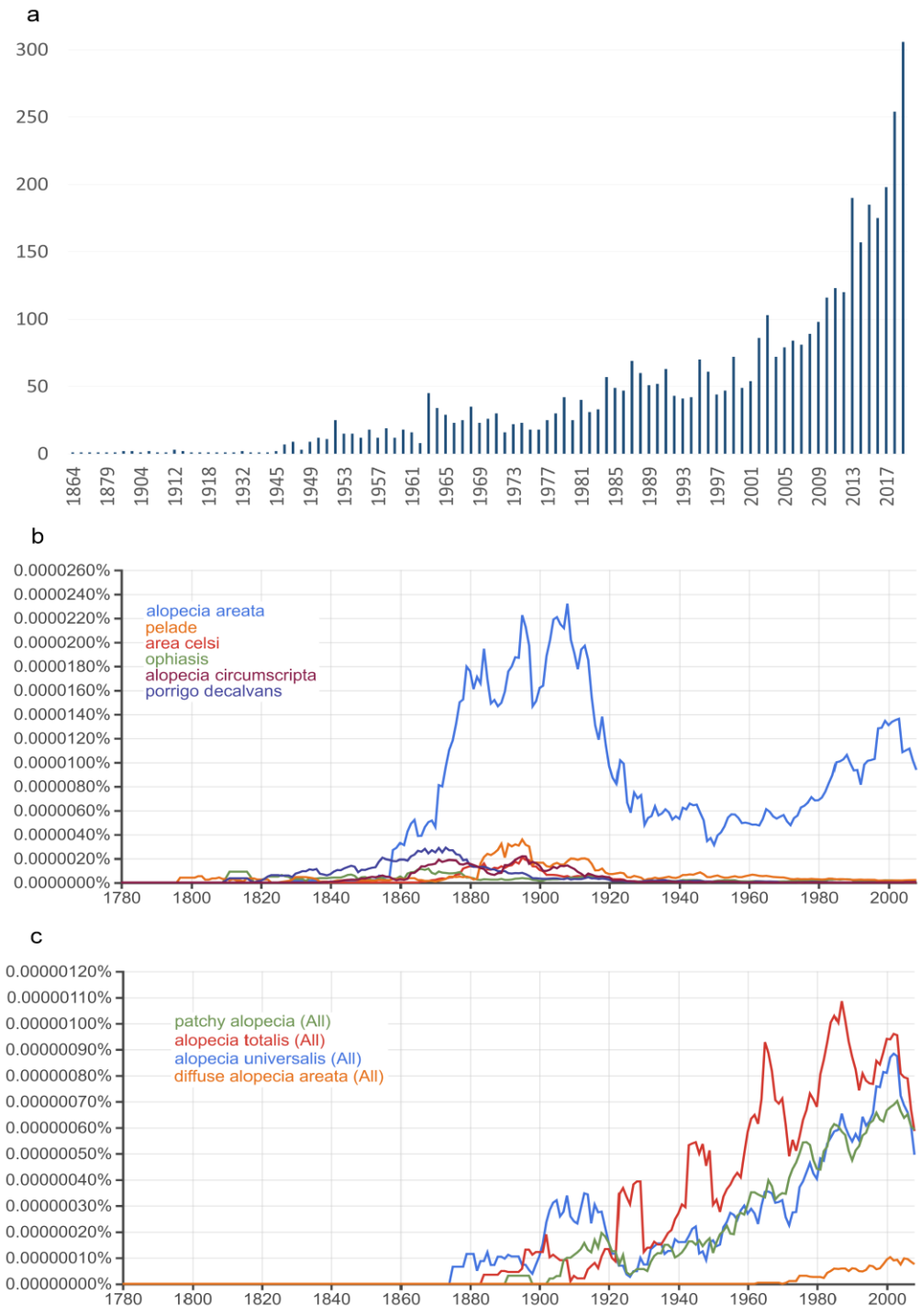

Fig 1. Changes in AA description in medical texts over time. (a) A progressive increase in the number of AA related manuscripts published annually in peer reviewed journals by year to 2019. (b) Relative frequency of different names for AA in books over time using Google ngrams viewer. (c) Relative frequency of specific AA types in books over time using Google ngrams viewer.

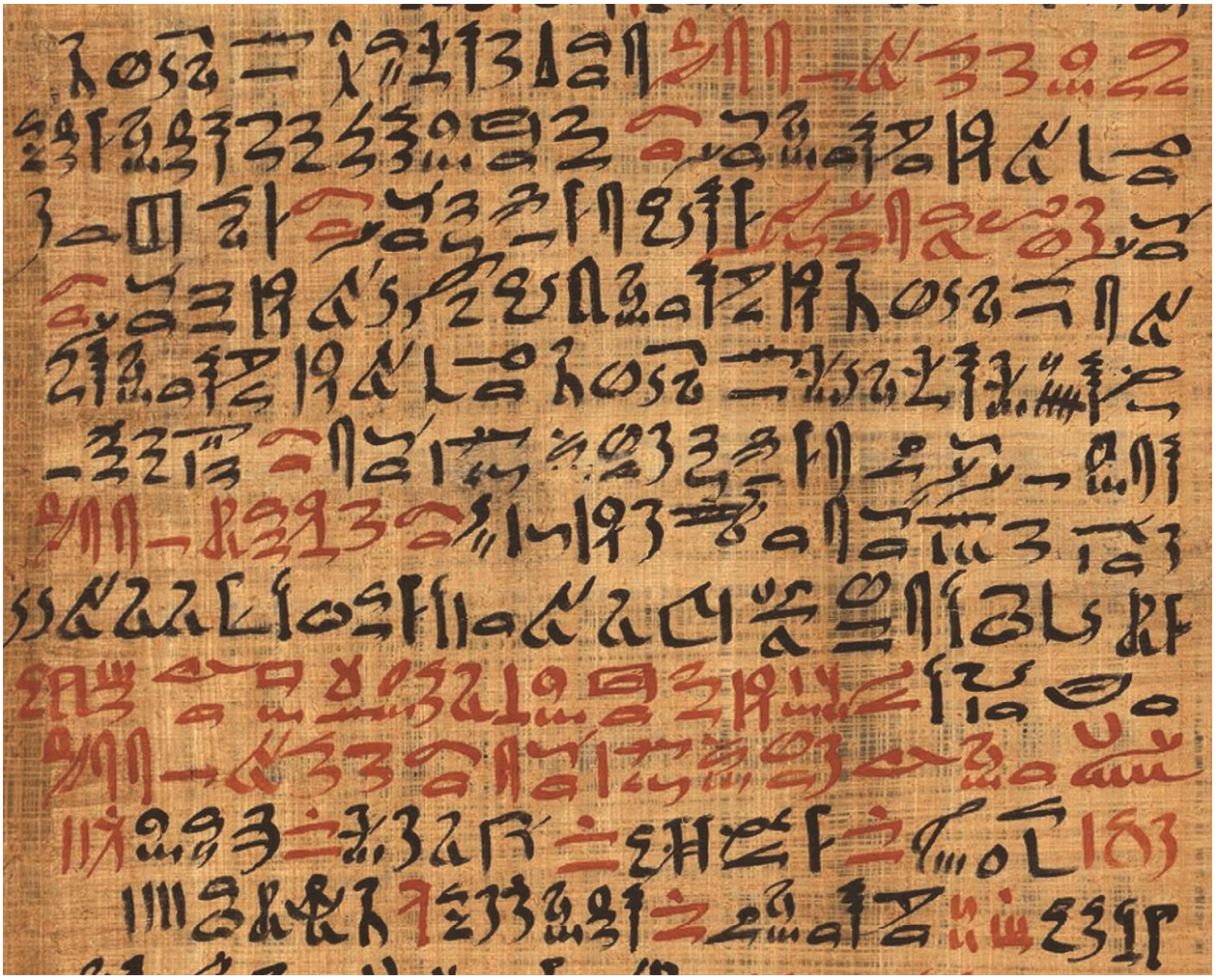

Fig 2. AA treatments in the Ebers papyrus. A section of the Ebers papyrus listing 6 treatments for alopecia areata (Eb 771-776). The first two lines state: “To make the hair grow for spotted baldness; burnt quills of hedgehog with oil, the head is anointed for four days” (Eb 771). Other AA treatments suggest rubbing a mixture of red ochre and beer into the scalp after scarification (Eb 772) and application of burnt flax plant mixed in oil with wasps’ “dung” (Eb 774) (Printed with permission, University of Leipzig, Germany).

Fig 3. Engraved, hand colored plate of a male with multiple patches of AA. From: Bateman T, Willan R. Delineations of cutaneous diseases: exhibiting the characteristic appearances of the principal genera and species comprised in the classification of the late Dr. Willan and completing the series of engravings begun by that author. Longman, Hurst, Rees, Orme, and Brown; 1817 (KM, personal collection).

a


REPOUSSE GARANTIE INFAILLIBLE
DES CHEVEUX BARBE, CILS & SOURCILS
TOMBÉS PAR PLAQUES OU COMPLETEMENT
PELADE
MARQUE DÉPOSÉE
MARQUE DÉPOSÉE
SI VOUS EMPLOYEZ
L'EAU DONNET
"ANTI-PELADE"
LA LOTION ET LE SAVON
ANTISEPTIQUES
OCTAVIA
MÉTHODE DU
Prof. O. Donnet
SPÉCIALISTE
PRODUITS GARANTIS INOFFENSIFS
DÉPÔT GÉNÉ: 114, Rue Montmartre, PARIS
VENTE au DÉTAIL

b

Fig 4. AA in France in the early 1900s. (a) French advertisement for an "antiseptic" treatment for AA (la pelade) by Prof. Donnet in 1901, available from his pharmacy at 114 Rue Montmartre, Paris (KM, personal collection). As part of a multi-step treatment system, antiseptic lotion was applied to the scalp twice per day and L'eau Donnet was applied to alopecia spots three or four times per day with a small brush. The cost for a large bottle (~0.5 liters) was 8Fr; 1-2 days average wage in French cities at the time.[188] (b) A satirical cartoon of a soldier with AA from 1915 (KM, personal collection).

Tables

Table I. A timeline of key developments in AA history

Year	Description	References
~1500 BCE	The *Ebers papyrus* is written by an unknown scribe; the first known historical record of AA as "*bite alopecia*".	[5,6]
~30 CE	Cornelius Celsus, in *De Medicina*, describes "*Alopekia*", bald areas which occurred in both the scalp and the beard; and "*Ophiasis*", bald areas that spread like the windings of a snake.	[9,10]
~600 CE	Chao Yuanfang, in his script *Treatise on the Origin and Symptoms of Diseases*, presents the first attempt to explain AA pathogenesis as an invasion by the evil wind spirits.	[73]
~980 CE	Hali Abbas (Ali Abbas al-Majusi), in his script *"Liber regalis"* (*al-Kitab al-Maliki*), categorizes AA as a form of leprosy and likens the nature of AA to snakes casting their skin.	[7,189]
~1170	The belief that AA is a form of leprosy persists and it is described as the "fox disease" by Roger Frugard.	[190]
1664	Johannes Jonston, in his text *Medicina Practica*, first uses the term "alopecia area".	[27]
1763	François Boissier Sauvages de Lacroix, in his book *Nosologia Methodica*, first uses the phrase "alopecia areata".	[28]
1813	Thomas Bateman, in his text *A Practical Synopsis of Cutaneous Diseases According to the Arrangement of Dr Willan*, publishes the first classification system based on the appearance of skin disorders. He describes the essential characteristics of AA in patches and cites Celsus.	[15]
1817	The first clinical visual representation of AA is published in *The Delineations of Cutaneous Disease* medical atlas.	[17]
1841	Erasmus Wilson, in one of four *Lectures on diseases of the skin*, makes the first recorded mention of inflammation in relation to AA, along with defective nutrition due to poor capillary supply.	[33]
1843	David Gruby publishes the first investigation demonstrating presence of "*Microsporum audouini*" around the hairs in AA patients and outlines the infectious agent hypothesis to explain AA pathogenesis.	[32]
1847	Pierre Louis Alphée Cazenave, publishes the first description of an association between AA and vitiligo; at the time thought to be of nervous origin.	[91]
1858	Felix von Bärensprung publishes the an investigation demonstrating nerve atrophy in AA affected skin associated with trophic nerve paralysis and defines the "trophoneurosis theory" to explain AA pathogenesis.	[24]
1881	Collier and other colleagues publish case reports describing physical trauma causing AA onset.	[10,191]

1881	Kinney and other colleagues publish case reports describing emotional distress and psychological trauma causing AA onset.	[106,192]
1882	Duckworth and Harris describe inflammatory cells in and around AA affected hair follicles, but dismiss the observation.	[127]
1886	Max Joseph presents the first investigation with an animal model of AA suggesting that patchy hair loss could be induced by cutting the spinal ganglia of the second cervical nerve in the necks of cats.	[93,94]
1891	Sébastien Giovannini identifies focal inflammation in and around AA affected hair follicles and hypothesizes an inflammatory mechanism of AA development.	[129]
1902	Lucien Jacquet presents an explanation for the neuropathic theory of AA identifying nerve irritation caused by defective and diseased teeth.	[97]
1912	Adamson and colleagues develop a hypothesis of AA pathogenesis based on toxins inducing hair loss.	[112,114,115]
1913	Sabouraud and colleagues publish reports of AA association with endocrine gland disorders, particularly the thyroid.	[120-122]
1950	A clinical data study by Anderson identifies increased psychosomatic stress in relation to AA onset.	[107]
1958	Rothman, in discussion of a presentation on AA by van Scott, hypothesizes that autoantibodies may attack hair follicles causing hair loss.	[134]
1963	A large scale epidemiology study by Muller and Winkelmann reveals several clinical associations with AA.	[193]
1965	Ikeda classifies four subtypes of AA, including “atopic AA”.	[194]
1971	Billingham and Silvers identify hair follicle “immune privilege” after observing that melanocyte allotransplants to anagen hair follicles avoided immune rejection.	[195]
1977	An association between HLA class I and AA is identified.	[196,197]
1985	HLA class II antigen expression is identified in AA affected hair follicles.	[155]
1990	Oliver and colleagues present the DEBR rat model of spontaneous AA.	[166,167]
1992	Gilhar and colleagues show plasma/autoantibodies from AA patients have little or no impact on hair growth.	[152]
1993	Interferon-γ is shown to be important for AA development by Gilhar and colleagues.	[163,198]
1993	Paus, Messenger and colleagues outline theories of AA pathogenesis based on the breakdown of hair follicle immune privilege leading to T cell inflammation.	[157,159]
1994	Sundberg and colleagues present the C3H/HeJ mouse model of spontaneous AA.	[168]
1995	Safavi and colleagues identify the lifetime risk for AA development using data from a large scale cohort.	[199]
1995	Tobin and colleagues identify hair follicle specific autoantibodies in blood plasma from AA patients.	[147-149,200]

1996	McElwee and colleagues show depletion of $CD4^+$ and $CD8^+$ T cells can restore hair growth in the DEBR AA model.	[169,170]
1998	Gilhar and colleagues show AA can be promoted by injection of T cells.	[164]
1998	McElwee and colleagues show AA can be transferred by skin grafting in the AA mouse model.	[174]
1999	Olsen and colleagues publish standardized clinical assessment investigational guidelines for AA.	[201,202]
2000	Freyschmidt-Paul and colleagues show blockade of T cell migration can prevent AA using the AA mouse model.	[178]
2001	Gilhar and colleagues show AA can be promoted by injection of T cells activated by melanocyte derived epitopes.	[165]
2003	David Whiting establishes the histologic features of AA in scalp biopsy specimens taken from different patterns and stages of AA and defines different patterns of hair follicle dystrophy.	[203]
2008	Ito and colleagues show that abnormal upregulation of MICA expression in AA hair follicles leads to them being attacked by $NKG2D^+$ cells.	[204]
2010	Kang and colleagues demonstrate changes in immune privilege markers can occur in hair follicles from AA affected patients in overtly unaffected scalp skin areas.	[205]
2010	Petukhova and colleagues publish genome wide association studies (GWAS) identifying multiple susceptibility loci related to both the adaptive and innate immunity in AA patients.	[206]
2014	Bertolini and colleagues identify a role for mast cells in AA pathogenesis.	[207]
2016	Wang and colleagues demonstrate enrichment in the autoreactive T cell population of AA patients for both melanocyte and keratinocyte derived epitopes.	[153]
2018	A potential role for miRNAs in AA pathogenesis is suggested. So far, only miR-30b has been shown to play a role in AA development.	[185]

Table II. A timeline of treatment development in AA history

Year	Treatment description	References
~1500 BCE	The *Ebers papyrus* recommends; burnt flax plant mixed in oil with wasps' "dung"; a carob, alabaster, and honey mixture, made while chanting a prayer to the sun god; and various other treatments.	[5,6]
~20 BCE	Queen Cleopatra, in *De Ornatu*, suggests grinding up the heads of flies and rubbing them on the affected skin. Alternatively, (as cited by Bonham in 1630) Cleopatra recommends shaving the scalp, rubbing it with a linen cloth, and anointing the area with a soda alkali compound.	[25,55,56]

~30 CE	Celsus, in *De Medicina*, recommends; scarifying bald patches with a scalpel and that; "some are painting on caustics mixed with oil, and especially burnt papyrus; some turpentine-resin with fennel". Shaving daily with a razor to remove the surface skin and exposing the hair roots while continuing the treatment. After the initial hair growth response occurs, Celsus suggests a maintenance treatment applying Indian ink.	[9]
~60 CE	Pliny the elder recommends onion mixed with honey or vinegar.	[208]
~70 CE	Dioscurides suggests topical application of tar oil mixed with barley flour.	[208]
~150 CE	Antyllus (as cited by Rhazes (Abu Bakr Muhammad ibn Zakariya al-Razi)) defines scarification, cupping, and leeches for AA.	[209]
~190 CE	Galen indicates massaging the scalp, then rubbing onion onto the skin. Also, puncturing the affected skin area before applying a mixture of crushed onion mixed with honey. Alternatively, shaving the head, applying mustard plasters to trigger skin redness, massaging the skin and then applying tar, cedar oil, fig leaves, or onion.	[210]
~660 CE	Paulus Aegineta specifies removing any remaining scalp hair with sodium nitrate, rubbing with a woollen cloth to make the skin red and then applying the burnt shells of sea urchins mixed with bears grease.	[209]
~1000	Alsaharavius (Abu al-Qasim Khalaf ibn al-'Abbas al-Zahrawi al-Ansari) directs purging and applying a compound of mustard seed, euphorbium, pellitory, nettle-seed, oil of sesame, or pitch.	[209]
~1100	Avenzoar (Ibn Zuhr) endorses purging, regulating the diet, and oil of nuts and cherva.	[209]
~1127	Stephen of Antioch, in his translation of *Liber regalis* (*al-Kitab al-Maliki*) by Hali Abbas, reports bloodletting, pills and purges for treating AA.	[12]
~1150	Maimonides (Moses ben Maimon) suggests ground adder skin mixed with honey.	[211]
~1170	Roger Frugard advises "sweet and sticky" medicines, bloodletting, scarification, and cautery.	[190]
1363	Guy de Chauliac in his book *Chirurgia magna*, originally published in 1363, records several treatments for AA attributed to scholars from ancient Greece and the Middle East. One credited to Archigenes of Syria involved a mixture of juniper, myrrh, and wormwood bitters, mixed with wine and oil, fermented for five days, and applied to the scalp.	[212]
1558	Gessner, in his text *Historia animalium*, advises dung of mice or weasels applied to the head cures the "foxes evil". Attributed to ancient Egyptian texts.	[54]
1564	Ferrier advocates compound of rametti tree vines, bilberry, pine bark, and white roses; and with an alternative combination of oil of myrrh, aloes wood (resin), bark, tamarisk, wine and white clover.	[213]

1657	Vigier praises laxative pills for AA, taken once a day and made from rhubarb, oriental senna, and marine cabbage.	[214]
1731	Turner variously puts forward rubbing with a coarse linen cloth, fig-leaves, and onions to make the skin "wax red", leeches, scarification, or acupuncture, followed by labdanum resin, pigeons-dung, delphinium plant seeds, bay leaf oil, turpentine and wax. Indeed, anything "which may excite or stir up the heat" and attract "nourishment to the parts" for treating AA.	[57]
1836	Bateman proposes regular shaving, using friction, and oil of Mace dissolved in alcohol or prepared with tar oil, bitumen, camphor, or turpentine for AA.	[58]
1841	Wilson points to camphor, cantharides, and lavender oil. Or alternatively, iodine and antimony, for AA.	[33,215]
1864	Watson reports on the use of carbolic acid to treat AA topically, as well as iron and quinine supplements orally.	[216]
1873	Fox endorses mercury ointment and cantharides for AA.	[31]
1882	Thin presents case reports on the use of sulphur ointment for AA.	[217]
1930s	Chrysarobin, croton oil, formaldehyde and numerous other acidic and caustic chemicals are recommended for blistering the skin as a treatment for AA by various practitioners.	[59-61]
1952	Wilson successfully treats AA patients with adrenocorticotropic hormone (ACTH).	[218]
1952	Dillaha and Rothman first use oral systemic cortisone acetate to successfully treat AA. The mechanism of efficacy is unknown.	[66,67]
1955	Rony and Cohen first use local intradermal injections of hydrocortisone to successfully treat AA. The mechanism of efficacy is unknown. They also use topical fluoroeortisone acetate ointment, but without success.	[219]
1958	Kalkoff and Macher confirm that the local injection of hydrocortisone causes the peribulbar inflammatory cell infiltrate to disappear in AA.	[220]
1977	Dinitrochlorobenzene (DNCB) is first used to treat AA by Frentz, Happle, and colleagues.	[62,221]
1978	Braun-Falco and colleagues use UVA light and psoralen (PUVA) to treat AA.	[222]
1979	Braun-Falco and colleagues treat AA by anthralin-induced dermatitis.	[63]
1980	Happle and colleagues successfully use squaric acid dibutylester (SADBE) to treat AA.	[64]
1981	Weiss and colleagues use minoxidil to treat AA.	[223,224]
1983	Happle and colleagues first use diphencyprone (DCP) to treat AA.	[225]
1986	Systemic cyclosporin is used successfully for the treatment of AA.	[226-229]
1997	Topical FK506 (tacrolimus) is shown to be a promising treatment for AA in the rat model, however, in human studies this has not been the case.	[173,177]
2004	TNFα inhibitors, etanercept, infliximab, and adalimumab are	[230-232]

	suggested not to be effective treatments for AA and may even exacerbate the condition.	
2005	Heffernan and colleagues use alefacept to treat AA.	[233]
2006	Kaelin and colleagues treat AA with efalizumab.	[234]
2006	Joly uses methotrexate alone and in combination with corticosteroids to treat AA.	[235,236]
2013	Gilhar and colleagues suggest a potassium channel Kv1.3 blocker, PAP-1, could be a promising immunotherapy for AA.	[237]
2014	Clynes, Christiano and colleagues indicate JAK inhibitors, including baricitnib, tofacitinib and ruxolitinub, are promising treatments for AA.	[238-240]