INTRODUCTION

“Uncertainty is an uncomfortable position. But certainty is an absurd one.”

Voltaire (1674–1778)

The denial of uncertainty, the inclination to substitute certainty for uncertainty, is one of the most remarkable human psychological traits. It is both adaptive and maladaptive, and therefore, guides and risks to misguide. When physicians shift from a theoretical discussion of medicine to its practical application, they do not acknowledge the uncertainty inherent in what they do. There are aspects to human biology and physiology that just are not predictable. Doctors, like everyone else, display certain psychological characteristics in the face of uncertainty. There is the overconfident mindset: people convince themselves they are right because they usually are. However, biology, particularly human biology, is inherently variable. One would think that primary care physicians, such as general practitioners, grapple most with uncertainty. The truth is that specialization in medicine often confers a false sense of certainty. Physician’s denial of awareness of uncertainty serves similar purposes: it makes matters seem clearer, more understandable, and more certain than they really are, ultimately it aims at making action possible.¹

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On the occasion of the 18th Meeting of the European Hair Research Society, May 18–20, 2018, in Bologna, Italy, a lecture was given in the session “Alopecia areata (AA): From bench to clinic” with the title “The fascinating story of how Janus kinase (JAK) inhibitors became the drug of choice for AA.” The fact is that the JAK inhibitors may well have a robust scientific background, and on the basis of preliminary studies represent promising agents for the treatment of AA; however as yet, they cannot be considered drug of choice for the treatment of AA for a number of reasons.

AA is a common hair loss condition with a lifetime prevalence of approximately 2%[3] that is characterized by acute onset of nonscarring hair loss in usually sharply defined areas.[4] Some patients lose hair in only a small patch, while others have more extensive or less frequently diffuse involvement.[5] Occasionally, AA may progress to complete baldness, which is referred to as alopecia (areata) totalis (AT). When the entire body suffers from complete hair loss, it is referred to as alopecia (areata) universalis (AU). By the nature of its autoimmune origin, AA tends to be a chronic and recurrent disease. Depending on its acuity and extent, hair loss is obviously an important cause of anxiety and disability.

The course in the individual patient is unpredictable, although a large surface area, a long disease duration[6,8] and associated nail abnormalities[8] have a negative impact on prognosis, as well as may comorbidities such as atopic disease and possibly others.[9-11]

Spontaneous remission rates for patchy AA are 30%–50% within the first 6–12 months of disease onset, and 66% of patients will show complete regrowth of hair within 5 years. The overall incidence rate of relapses is 85%, and in patients observed over 20 years practically 100%.[10] If AT develops, 75% remain AT, 22.5% eventually develop partial AA, and 2.5% become normal.[4] In case of AT/AU, periods of significant hair regrowth may occur in 34% of adults and in 44% of children. Complete permanent regrowth of hair occurs in 10% of adults and in 1% of children.[4] Finally, female individuals usually older than 20 years of age who rapidly lose their hair in a diffuse manner (acute diffuse and total alopecia of the female scalp) tend to have a short clinical course with a favorable prognosis, ranging from acute hair loss to total baldness, and followed by rapid regrowth of hair usually within 6 months.[12]

A meta-analysis of published trials on the treatment of AA states that only few treatments have been well evaluated in randomized trials.[13] most trials have been reported poorly and are so small that any important clinical benefits are inconclusive. The authors concluded that considering the possibility of spontaneous remission, especially for those in the early stages of the disease, the options of not being treated or, depending on individual preference, and of wearing a wig may be alternative ways of dealing with the condition.

Moreover yet, from clinical practice, we know that depending on patient age, surface area, disease duration, and comorbidities an empiric treatment algorithm can be designed that is successful in a significant proportion of patients [Figure 1].[13]

Accordingly, single patches of AA are best treated with intraleisonal triamcinolone acetonide (ITA) in a concentration between 2.5 mg/ml (eyebrows and beard area) to a maximum of 10 mg/ml (scalp), depending on the localization, by jet injector or insulin syringe (frontal and temporal regions, eyebrows, and beard area) at 4–6 weeks’ intervals, as long as needed.[14] Since patchy AA is the most prevalent form of the disease, and ITA the most frequently practiced treatment for this condition. In an attempt to circumvent side effects related to the use of corticosteroids. Chu et al.[15] evaluated the benefit of different concentrations (2.5, 5, and 10 mg/mL) of ITA in AA, and did not find any difference in regrowth of hair between the different concentrations, enabling injection of larger surfaces at lower concentrations, and lesser cumulative doses of triamcinolone acetonide.

Acute and widespread AA (>30% surface area) is best treated with systemic corticosteroid therapy either orally or intravenously. Again, in an attempt to circumvent side effects related to systemic corticosteroid use, the pulsed administration has been proposed for the treatment of AA. Kar et al.[16] confirmed in the first placebo-controlled study usefulness of oral prednisolone pulse therapy in AA. Agarwal et al.[17] alternatively suggested twice weekly 5 mg betamethasone oral pulse therapy on 2 consecutive days per week for a total duration of 12 weeks. To determine the effectiveness of intravenous pulse therapy in AA, much in the same manner it is performed for the treatment of other autoimmune diseases, Friedli et al.[18] originally performed an open prospective study of patients with rapid and extensive hair loss (>30% scalp area) for <1 year (first occurrence or relapse). 250 mg intravenous methylprednisolone (IV-MPPT) was administered twice a day on 3 consecutive days. A single series of IV-MPPT was well tolerated and appeared to
be effective in patients with rapidly progressing extensive multifocal AA, but not those with ophiasic and AU. Subsequently, Nakajima et al. confirmed the efficacy of IV-MPPT in a larger study of patients aged >15 years with AA. With IV-MPPT (500 mg methylprednisolone on 3 consecutive days, in three cycles, 4 weeks apart) within 6 months of disease onset, remission rates were 88% for multilocular AA with surface area <50%, 59.4% with surface area >50%, and 21.4% in AT/U. Performed after 6 months of disease onset, the remission rate decreased to 15.8%. The prognostic factors that influenced the successful outcome of IV-MPPT for AA were disease duration before the treatment in relation to the type of AA. A good response was obtained for all types of AA with a duration of 3 months or less before treatment, and for the multifocal type of AA with a duration of <6 months. The patients who responded to the treatment had low relapse rates suggesting that in patients with good prognostic factors, IV-MPPT may be beneficial.

New drug treatment opportunities based on the results of genome-wide association studies that implicate T cell and natural killer cell activation pathways are paving the way to new targeted approaches for the treatment of AA. Currently, there are ongoing studies with the CTLA4-Ig fusion protein abatacept (blocks costimulation of T cells), anti-IL15Rb monoclonal antibodies (blocks activation of CD8+ T cells), and JAK inhibitors (block signal transduction at the IL-15 receptor).

Craiglow and King originally reported hair growth in a patient with AU treated with the JAK inhibitor tofacitinib for plaque psoriasis. Xing et al. subsequently reported successful treatment of three patients with AA with oral ruxolitinib. The patients achieved near-complete hair regrowth within few months of treatment, suggesting the potential clinical utility of JAK inhibition for the treatment of AA. Jabbari et al. reported a reversal of AA in a patient treated with oral baricitinib for chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome. Ultimately, Liu et al. conducted a retrospective study of patients’ age 18 years or older with AA with at least
40% scalp hair loss treated with tofacitinib. The primary endpoint was the percentage change in the severity of alopecia tool (SALT) score during the treatment. A total of 90 patients met the inclusion criteria. Of 65 potential responders to therapy, defined as those with AT or alopecia universalis with the duration of current episode of disease of 10 years or less or AA, 77% achieved a clinical response, with 58% of patients achieving >50% change in SALT score over 4–18 months of treatment. Patients with AA experienced a higher percentage change in SALT score than did patients with AT/U (81.9% vs. 59.0%). Tofacitinib was well tolerated, and there were no serious adverse events. In an attempt to evaluate the benefit and adverse effects of the tofacitinib in a series of adolescent patients with AA, Craiglow et al.[31] reviewed the records of 13 adolescent patients aged 12–17 years with AA treated with tofacitinib. Nine patients experienced clinically significant hair regrowth with a median percentage change in SALT score of 93% at an average of 6.5 months of treatment. Adverse events were mild.

Nevertheless, at this time point, affordability of the JAK inhibitors for long-term treatment, sustainability of treatment result,[32] long-term safety, and liability of the physician prescribing the drug off label[33] are major issues with regard to the treatment of AA with JAK inhibitors, unless patients are enrolled in ongoing clinical studies with either of the JAK inhibitors.

Finally, the sophisticated treatment of such a multifaceted disease as AA cannot be reduced to one drug, while in many patients – depending on disease duration and surface area - either IV-MPPT, ITA, or MTX will achieve remission rates in the range of the efficacy of the JAK inhibitors. Ultimately, the options available for adapting to the disease rather than treating it in an effort to cure may also be taken into consideration in selected cases of long-standing or recurrent small spot disease.

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Conflicts of interest
There are no conflicts of interest.

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