

The Use of Sulfasalazine in Severe Types of Alopecia Areata

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Abstract

Extensive types of alopecia areata (AA), especially alopecia totalis (AT) and alopecia universalis (AU) are notoriously difficult to treat. Recently, sulfasalazine has shown a promising result with well-tolerated side effects through immunomodulatory and anti-inflammatory effects. Several studies reported desirable response among AA patients who failed other treatments. This article reviews the previous studies of sulfasalazine in AA in terms of its efficacy as well as other aspects including mode of action, indications, contraindications, dosage, administration, drug interaction as well as monitoring.

Keywords: Alopecia areata; Sulfasalazine; Hair loss

Abbreviations: AA: alopecia areata; AT: Alopecia Totalis; AU: Alopecia Universalis; IL: Interleukin.

Introduction

With prevalence ranging from 0.7 % to 3.8% of patients attending dermatology centers in different populations, [1,2] alopecia areata is undoubtedly a common disease. There is no sex or ethnic predilection and it may occur at any age, however, the majority commence before 20 years [3]. Intriguingly, up to 85% of Asian patients develop AA before 40 years of age [4]. Although the majority of patients present with a sudden onset of patchy hair loss that re-grows spontaneously without any scars within a year [5,6], AA in up to 10% of patients may progress into more chronic and extensive forms [5].

Despite its commonness, the exact pathophysiology of AA remains largely unknown. At present, it is believed to be an autoimmune and inflammation-driven disease. Hence, it is commonly associated with myriads of other autoimmune conditions including thyroid diseases, e.g. Graves's disease and Hashimoto's thyroiditis [7,8], vitiligo [9], diabetes as well as myasthenia gravis [10].

The loss of hair in AA is related to alterations in the normal cycle of hair growth, with shifting of follicular stages from anagen to catagen, and in turn telogen. Typically, miniaturized hair follicles and inflammatory infiltrates comprising predominantly lymphocytes at peribulbar region are seen on histology [11-14]. CD₄ and CD₈ T cells are believed to be involved in this mechanism and the extents of hair loss have been shown to correlate with the ratio of these cells [15]. Moreover, both cell subsets are involved in AA induction and persistence, at least in the mouse models [16,17].

Besides T cells, several clinical and experimental studies point toward defects in cytokine production or signaling that might induce hair loss in AA, the processes in which interleukin (IL) -1 [18], -2 [19], -6 [20] and tumor necrosis factor alpha (TNFα) [18] have been demonstrated to be involved. Recently, the pathogenesis of AA has been extensively reviewed by Alkhalifah et al. [21]

Widely-used modalities of treatment include corticosteroids in virtually all modes of administration, topical sensitizers, anthralin, minoxidil, PUVA and even 308-nm excimer laser. However, none of these has yielded consistent results and the recalcitrant and extensive AA, especially AT and AU are notoriously difficult to treat. Recently, sulfasalazine was described in a few reports with promising outcomes in these perplexing types of AA [22-26].

History

Sulfasalazine was first developed in 1938 for the treatment of

rheumatoid arthritis [27] for which it is now categorized as a disease-modifying antirheumatic drug (DMARD). It is also used in various diseases in which T lymphocytes are involved in pathophysiology such as inflammatory bowel disease, psoriasis and scleroderma among others.

Mode of action of sulfasalazine

Although sulfasalazine has been used for many decades, the precise mechanism of action has not been fully elucidated, nor is it clear whether the parent drug and/or its metabolites, namely sulfapyridine and 5-aminosalicylic acid, are principally responsible for its beneficial effects. Following oral administration, the pro-drug is inactive. Only upon reaching the colon where it is degraded by bacterial azoreductases, is when sulfapyridine and 5-aminosalicylic acid released. All 3 moieties, i.e. sulfasalazine, sulfapyridine and 5-aminosalicylic acid, are extensively metabolized.

The action of sulfasalazine in autoimmune diseases is most likely mediated by either immunomodulatory or anti-inflammatory effects [28]. For immunomodulatory effects, several *in vitro* studies have shown that sulfasalazine and/or its metabolites inhibit the release of cytokines produced by various cell types, especially T-lymphocytes which are responsible for IL-2 induction and monocytes/ macrophages, responsible for IL-1, IL-6, IL-12 and tumor necrosis factor (TNF)-α induction [29-31]. Possibly through regulations of these cytokines, as well as T-cell proliferation, natural killer cell activity and activation of B cells, sulfasalazine halts AA progression [28].

For anti-inflammatory effects, sulfasalazine has been shown to inhibit chemotaxis and random migration of inflammatory cells such as neutrophils, and reduce superoxide and proteolytic enzyme production [28]. An *in vitro* study suggested sulfasalazine might also exert a slight inhibitory effect by modulating prostaglandin E₂ synthetase activity [29].

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Received September 26, 2011; **Accepted** October 31, 2011; **Published** November 23, 2011

Citation: Chairerg P, Asawanonda P, Kongkabpan M, Suwanwalaikorn S, Taungjaruwina WM (2011) The Use of Sulfasalazine in Severe Types of Alopecia Areata. Hair : Therap Transplantat 1:102. doi:10.4172/2167-0951.1000102

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Indications and contraindications

The challenge of AA treatment is the fact that although many treatment modalities are available, none can change its natural course. Safety of the medication when used long-term is thus, of utmost importance. In this regard, sulfasalazine may have an important role as there are reports on successful and safe use of sulfasalazine in inducing hair regrowth in AT and AU in both adults and children [22-26]. It has also been used as a sole agent in the maintenance phase of treatment.

Contraindications and warnings/precautions for the use of sulfasalazine in the treatment of AA are summarized in Table 1.

Therapeutic efficacy of sulfasalazine for AA

In an extensive records review by Ellis et al., wherein 16% of 249 evaluable AA patients were treated with sulfasalazine, cosmetically acceptable hair regrowth took place in 23% of the subjects [24]. Among those who completed a course of sulfasalazine, 80% with limited AA had excellent benefit while only 21.43% of patients with AT/AU had similar responses. Complete regrowths were also observed [26]. In 2008 Aghaei and co-workers from Iran reported the efficacy of sulfasalazine in 22 evaluable patients with recalcitrant AA or severe AA with more than 40% hair loss, in an open-label study. The duration of treatment ranged from 6 to 24 months, including some patients who required long-term treatments to maintain hair regrowth. Approximately two-thirds of the patients responded to treatment, among these 27.3% showed complete hair regrowth. In all, 36.4% of treated subjects had 50% hair regrowth or more [22]. The largest prospective study was also reported from Iran in the same year. Using the very same protocol, Rashidi et al. demonstrated the efficacy of sulfasalazine in 39 patients with alopecia areata in whom 43.6% had 50% hair regrowth or more. When different extents of AA were analyzed, 51.7% with patchy alopecia had 50% hair regrowth whereas only 20% of AT patients had such results [26]. The authors also pointed out that patients whose disease onset was during childhood had less favorable response to the treatment. Despite the successful treatment, hair loss recurred in 25% to 45.5% of cases in the above studies. This usually took place a few months after termination of therapy [22,26] but had also occurred even during maintenance treatment [22].

Apart from the extent of hair loss and age at onset, which are the 2 most predictive prognostic factors in AA, it is clear from the above-mentioned reports that response to sulfasalazine seems to be somewhat dose-dependent. In many subjects in Ellis and co-workers' report, the response was not seen at dosages under 3g/day. Moreover, when doses were reduced hair loss ensued and stopped when doses were escalated [24]. This agrees well with our experience. Also, the duration

of treatment is of importance, as hair regrowth often takes 3-5 months to occur or to be cosmetically appreciated [23,24].

It is rather difficult to compare the results of sulfasalazine with other therapeutic agents due to the paucity of information in the English literature. Most reports on systemic agents as monotherapy comprise only case series, whilst in others they are used in combination with corticosteroids [32]. However, sulfasalazine seems to compare favorably with cyclosporine monotherapy [33].

Dosage and administration

Sulfasalazine is available in an oral form as 500mg enteric-coated tablets. Gradual dose escalation is desired to minimize gastrointestinal side effects. In rheumatoid arthritis, sulfasalazine is started at 500 mg/day and increased weekly to optimal therapeutic range at 2-3 g/day taken twice a day, preferably with meals. Among AA studies, most patients are initially prescribed at a dosage of 1 g daily with increments of 1 g monthly until optimal doses of 3-4 g/day are reached. If the result is desirable, it can be maintained at these dosages for at least 3-7 months [22,23,25,26]. However, some authors recommend more rapid dose escalation such as weekly as employed in rheumatoid arthritis [24].

Combination therapy: Corticosteroid is commonly used as a first drug to halt the progression of active AA, however, high relapse rate after discontinuation and long-term side effects are valid concerns. One strategy to lessen relapse after discontinuation is combination with sulfasalazine. This combination is logical as the 2 agents have different mechanisms of action and more importantly, distinct adverse effect profiles. In a report by Bakar and Gurbuz, 6 patients with AA resistant to previous treatments with a range of disease duration from 3 to 20 years, were treated with sulfasalazine in combination with oral corticosteroids with desirable outcome [23]. Duration of the combination was 2-6 months, following which the corticosteroids were withdrawn and sulfasalazine monotherapy ranging from 4 to 12 months was used to sustain the initial hair regrowth. Interestingly, some patients maintained the regrowth hair after discontinuation of sulfasalazine. No severe side effects were detected [23]. Although there are limited data of this combination it should be considered as an alternative choice for refractory disease.

Drug Interaction

Drug-drug interaction

Sulfasalazine reduces absorption of digoxin resulting in decreased effectiveness of the latter. When sulfasalazine is combined with sulfonylureas special attention needs to be paid due to decreased elimination of the hypoglycemic agents by the liver resulting in excessive reductions in plasma glucose. The risk of kidney damage from cyclosporine increases when it is combined with sulfasalazine by unknown mechanisms. A byproduct of sulfasalazine, sulfapyridine, increases blood levels of methotrexate contributing to increased methotrexate toxicity. Moreover, methotrexate can worsen anemia caused by sulfonamide as both deplete folates. Sulfapyridine also enhances the anticoagulant effect of warfarin resulting in deterioration of controlled international normalized ratio (INR) level. As a result, close monitoring of anticoagulant activity is necessary for this combination. Paradoxically, there is a case report of recurrent deep-vein thrombosis due to warfarin resistance in ulcerative colitis treated with sulfasalazine [34] (Table 2).

Combining 5-aminosalicylic acid with nonsteroidal anti-inflammatory drugs may increase the risk of renal dysfunction. Lastly,

Contraindication:

- Hypersensitivity to sulfonamides or salicylates
- Age < 2 years
- Gastrointestinal tract/Genitourinary tract obstruction
- Porphyria

Warnings/precautions:

- Bloody dyscrasia
- Hepatic impairment
- Renal impairment
- Severe asthma
- Pregnancy and lactation
- G6PD deficiency

Table 1: Contraindications and warnings/precautions for sulfasalazine.

concurrent use of 5-aminosalicylic acid and 6-mercaptopurine or azathioprine could result in higher risks of bone marrow suppression [35,36].

Drug-food interaction

Sulfasalazine decreases folic acid absorption from food which may cause folate deficiency and result in anemia [37,38]. One mg/day of folic acid is, therefore, recommended for those taking sulfasalazine to prevent anemia.

Adverse Effects

Sulfasalazine has a relatively good safety profile. Adverse effects in most cases occur in the first 3 months of therapy and are well-tolerated [39,40] (Table 3). Nevertheless, approximately 20-30% of patients encountered adverse events severe enough to result in discontinuation of treatment [24,29,40]. Fatal side effects of sulfasalazine are rare and usually develop within 2-6 weeks after initiation of the medication. These include the “three-week syndrome”, which is characterized by fever, lymphadenopathy and widespread erythematous rash, followed by severe hepatotoxicity [40]. The more serious reaction, DRESS syndrome, does not occur frequently, however, physicians should perform a close observation especially during the early phase of therapy [40,41].

Many side effects are associated with high serum levels of sulfapyridine which depends on acetylator phenotype [39,42]. Common side effects are gastrointestinal disturbances (nausea, vomiting, dyspepsia, diarrhea, decreased appetite, anorexia) and central nervous system effects (dizziness and headache) which account for 66.6% of the reported adverse events in a large prospective study [43]. Skin eruption is reported in 4-5% of patients taking sulfasalazine [24,44]. Hematologic dysfunctions, e.g. leucopenia are reported in less than 3% of sulfasalazine recipients. However, up to 50% of those patients who received high dose sulfasalazine (4-6 gm/day) demonstrate evidence of hemolysis [39]. Photosensitivity has been reported in rare cases. Other less common adverse effects include various blood dyscrasias, fever, arthralgia, dyspnea and hepatic dysfunctions.

Sulfasalazine and sulfapyridine can cross the placenta. Sulfasalazine is US FDA pregnancy risk categories B and D if administered near-term. Nevertheless, it is not contraindicated in pregnant women. A study by Norgard et al. demonstrated no significant increases in the risk of fetal malformations in pregnant women with ulcerative colitis treated with sulfasalazine [45]. Thus, sulfasalazine may be used in pregnant women if the benefits outweigh the possible risks. Sulfonamides are excreted in human breast milk, which can theoretically induce kernicterus in the newborn. However, this risk is low at therapeutic doses.

Drugs	Effects
Azathioprine (Imuran)	Increased risk of bone marrow suppression
Cyclosporine	Increased risk of kidney damage
Digoxin	Decreased effectiveness of digoxin
Hypoglycemic agents (sulfonylurea)	Excessive reductions in blood sugar
Methotrexate	Increased methotrexate toxicity and increased risk of folic acid deficiency
Nonsteroidal anti-inflammatory drugs	Increased risk of kidney damage
Warfarin	Interferes with anticoagulant effects
Folic acid	Decreased folic acid absorption from food

Table 2: Drug interactions of sulfasalazine.

Common

Gastrointestinal tract disturbances (nausea, vomiting, dyspepsia, diarrhea)
Central nervous systemic effects (headache, dizziness)

Less common

Hematologic abnormalities (leucopenia, neutropenia, thrombocytopenia, macrocytosis etc.)
Hepatotoxicity (elevate liver enzymes, liver failure)
Fever
Reversible male infertility
Systemic reaction (DRESS syndrome, three-week syndrome)
Renal toxicity
Arthralgia
Acute hemolysis, especially in G6PD deficiency

Table 3: Side effects of sulfasalazine.

Reproductive dysfunction is also a relatively common side effect of sulfasalazine as well as an important concern for patients as it possibly leads to male infertility. Fortunately, this side effect is reversible after withdrawal of sulfasalazine for 14 days [46,47]. Impaired sperm motility or morphology and a decrease in the number of spermatid cells in the testis were found in male patients treated with sulfasalazine [46,48]. The mechanism underlying this complication is not clearly understood. An animal study suggested that sulfasalazine-induced oxidative stress may be responsible [46].

Laboratory Investigation

Besides close clinical observation, all patients taking sulfasalazine must be monitored with laboratory investigations to prevent early and delayed adverse effects. Complete blood count, liver function tests, blood chemistry profile, thyroid function tests, urinary analysis, antinuclear antibody (ANA), G6PD status and serological screening for syphilis are usually performed at baseline. During treatment, complete blood count and liver function tests should be performed every 2 weeks for 2 months and monthly for 4 months. After 6 months, if no change of the dosage is planned, complete blood count and liver function tests can be performed every 3 months.

Summary

Sulfasalazine can be a valuable alternative treatment option in AA patients who are resistant to other therapeutic modalities. It acts through immunomodulatory and anti-inflammatory effects. Sulfasalazine may be prescribed as monotherapy or combined with other therapies especially corticosteroid. Approximately one quarter of AA patients treated with sulfasalazine will achieve good to excellent response. Serious adverse reactions from sulfasalazine even in long-term use or when combined with other treatments are rare. However, a close clinical and laboratory monitoring is recommended especially at the initial period of treatment.

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