Treatment of Chronic Hand Eczema: Other Immunomodulating Therapies

96

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Contents

Abstract

The management of chronic hand eczema is challenging and includes several behavioral and medical measures. A subset of patient will not respond to topical treatment strategies alone, but may benefit from systemic therapy. In this chapter, selected immunomodulating

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drugs (azathioprin, cyclosporine, methotrexate) which have been successfully used for the systemic treatment of chronic hand eczema is reviewed regarding their clinical pharmacology, mechanisms of action, efficacy, and safety.

Keywords
Chronic hand eczema · Immunomodulating drugs · Methotrexate · Cyclosporine A · Azathioprine

1 Introduction

The management of chronic hand eczema is challenging and includes several behavioral and medical measures demanding a solid physician-patient relationship. Frequently, the clinician is faced with patients who do not respond to conservative measures, even when these are strictly followed. This patient population, which is associated with a significant, long-lasting decrease in quality of life and reduced performance at work, often frustrated after long years of fruitless treatment, is likely to benefit from systemic therapy. In the following chapter, selected immunomodulating drugs which have been successfully used for the treatment of chronic hand eczema will be reviewed.

2 Azathioprine

Azathioprine (AZA) is an immunosuppressive drug widely used in the first days of transplantation medicine which is currently prescribed for the treatment of a wide range of diseases including systemic lupus erythematosus, Crohn's disease, dermatomyositis, and bullous dermatoses, among others (Anstey et al. 2004). Additionally, since its availability in the 1960s, it has been used for several non-licensed indications, including severe atopic dermatitis (Wise and Callen 2007). As AZA therapy is not approved for the treatment of hand eczema, patients should be informed about the off-label character of the treatment.

3 Clinical Pharmacology

After absorption, AZA is rapidly converted to 6-mercaptopurine (6-MP) by universally present substances like glutathione and cysteine. Subsequently, 6-MP is converted by the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT) to its active metabolites, which are thought to exert the drug's immunosuppressive effect through the incorporation of thioguanine (TG) nucleotides into DNA. The half-life of these metabolites comprehends several days; a steady state is only reached after 2–4 weeks. Moreover, the accumulation of TG in cells takes place relatively slowly, explaining why the clinical effect is only seen after several weeks, with most clinicians reporting an onset of efficacy of about 12 weeks (Wise and Callen 2007; Sahasranaman et al. 2008).

The inactivation of 6-MP and most part of its metabolites is catalyzed by thiopurine methyltransferase (TPMT), an enzyme of relevance in clinical practice. It has been shown that pretreatment determination of TPMT and follow-up measurement of TPMT and some of its metabolites could assist therapeutic decisions in a clinical setting. A polymorphism in the TPMT gene for either high ($TPMT^H$) or low ($TPMT^L$) enzyme activity could explain why some patients do not respond to high doses of AZA, while others develop severe side effects, most importantly myelosuppression. It is estimated that approximately 10% of the population are heterozygous at the TPMT locus and that 0.33% are homozygotes for $TPMT^L$. Therefore, AZA should be given at lower doses for heterozygotes and avoided by patients presenting with TPMT deficiency. Analogue to glucose-6-phospate dehydrogenase (G6PD) measurement prior to therapy with dapsone, it is recommended to perform genotype screening for TPMT phenotype through PCR or to determine erythrocyte TPMT activity in patients about to commence AZA therapy in order to predict risk of toxicity or to avoid AZA prescription for TPMT-deficient individuals (Wise and Callen 2007; Sahasranaman et al. 2008).

AZA interacts with several prescription drugs. Of note, patients receiving allopurinol can present a fivefold increase in plasma concentration of AZA metabolites. Therefore, it is recommended to carefully exclude possible interactions between AZA and other substances before commencing treatment.

4 Mechanism of Action

It is believed that AZA exerts a cytotoxic as well as an immunosuppressive effect through mechanisms which have only been in part characterized. The incorporation of its metabolites into the DNA has been shown to promote cell-cycle arrest and apoptosis, a process well characterized in leukemia patients. Although these cytotoxic properties are desired in an oncological setting, it is the immunosuppressive effect of AZA which provides the rationale for the treatment of hand eczema. The metabolites of AZA have been shown to accumulate in T lymphocytes, leading to apoptosis in this cell population. Moreover, it has been shown that upon T-cell activation, the expression of inflammatory genes like TRAIL or TNFRS7 is inhibited. These events culminate in a T-cell-mediated immunosuppression (Wise and Callen 2007; Sahasranaman et al. 2008; Thomas et al. 2005).

5 Efficacy

Although systematic studies investigating the role of AZA therapy in the specific context of hand eczema are missing, several positive reports of its off-label use for the treatment of severe atopic dermatitis have been published (Anstey et al. 2004; Wise and Callen 2007; Verma et al. 2006, 2008). A study with a population of 37 patients presenting with severe atopic dermatitis reported a remission rate of 40.5% in a mean time of 5 months. There are controversial data in the literature concerning the dosage of AZA. Some investigators used a standard dosage of 100 mg per day; further studies described doses of 1.5–2.5 mg/kg per day. Determination of TPMT status is recommended before starting AZA treatment (Wise and Callen 2007).

6 Safety

Adverse events of AZA are divided into two types: idiosyncratic and dose dependent. Most common non-dose-dependent reactions include nausea, fever, rigors, arthralgias, rash, and rarely pancreatitis (Anstey et al. 2004; Wise and Callen 2007; Sahasranaman et al. 2008). Leukopenia is the most common dose-dependent side effect, and it is usually reversible after dose reduction. As discussed above, prospective testing for TPMT activity or TPMT genotype should identify patients at high risk for myelosuppression. Another relatively commonly observed phenomenon is a mild increase in transaminase levels which is also reversible after dose reduction. Another side effect associated with AZA treatment is an increased risk for malignancy. This was well documented in organ transplant patients who were treated with AZA along with other immunosuppressants over many years (Anstey et al. 2004; Wise and Callen 2007; Sahasranaman et al. 2008). These patients have an increased risk for squamous cell skin cancer and non-Hodgkin's lymphoma. Short treatment courses over less than 1 year do not seem to increase the risk of neoplasia. This was well documented in a population of over 16,000 inflammatory bowel disease patients, which presented no increased risk of lymphoma. It is unknown whether AZA increases the risk of cancer when prescribed for hand eczema patients, but it is likely that short courses of the drug are safe.

7 Cyclosporine

The clinical use of the immunosuppressant cyclosporine A (CsA) was established in the early 1980s for the treatment of organ transplantation recipients, causing an increase in overall survival in this patient population. Currently, CsA is approved and used not only in the treatment of various skin disorders, including psoriasis and

atopic dermatitis, but also autoimmune diseases such as lupus erythematosus (Griffiths et al. 2006; Mrowietz et al. 2009).

8 Clinical Pharmacology

CsA is a hydrophobic cyclic decapeptide consisting of 11 amino acid residues which was isolated from cultures of the fungus *Tolypocladium inflatum*. The low aqueous solubility and permeability of CsA are the physicochemical characteristics that explain the relatively low bioavailability of the drug. The first registered formulation is based in a simple oil-in-water system, which exhibits high intra- and interindividual variability. To overcome these unfavorable features, a newer formulation based on a microemulsion showing improved pharmacological characteristics was developed. Although the metabolism of the drug takes place mostly in the liver through the cytochrome P450 3A enzymatic system, this process may also take place in the gastrointestinal tract and the kidneys. This results in 15–30 metabolites which are reported to be less toxic than the original molecule (Griffiths et al. 2006; Mrowietz et al. 2009).

Since CsA has a very narrow therapeutic window, dosage should be adapted to the patient's weight. It is usually recommended an initial dose of 2.5–5 mg/kg per day. In patients showing an adequate response, the dose should be reduced to 0.5–1 mg/kg per day every 2 weeks. The CsA dose can be increased in patients failing to respond to the substance, up to a maximum of 5 mg/kg per day. CsA therapy should be interrupted in case of nonresponse after 12–16 weeks, adverse effects, serious infections, neoplasia, and pregnancy. Most hand eczema patients benefit from relatively short courses of CsA. Otherwise, hand eczema patients should not be treated with the drug over more than 6 months. In order to avoid a rebound effect, CsA therapy should not be interrupted abruptly. Drugs that inhibit or stimulate the cytochrome P450 system will alter the plasmatic levels of CsA so that co-prescription of these drugs requires caution (Griffiths et al. 2006; Mrowietz et al. 2009).

8.1 Mechanism of Action

CsA mechanism of action is mediated mainly through the suppression of T-cell functions. Upon entering the lymphocyte, CsA binds to cyclophilin, a cytoplasmic receptor protein which interacts with the phosphatase calcineurin. This complex binds to calcineurin and prevents calcineurin-mediated dephosphorylation of the cytoplasmic nuclear factor of activated T cells (NFAT), an event which blocks the translocation of this transcription factor into the nucleus. This leads to the blockage of the transcription of several T-cell-derived effector cytokines, potently inhibiting immune responses (Griffiths et al. 2006; Mrowietz et al. 2009).

9 Efficacy

There are few studies investigating the role of CsA in the treatment of hand eczema. A double-blind investigation by Granlund and colleagues comparing oral CsA (3 mg/kg/day) to a potent topical corticosteroid showed a reduction of 50% in disease activity in the cyclosporine group as compared to 32% in the topical steroid group. The long-term results were however disappointing, as 50% of patients showed a relapse after a follow-up period of 2 weeks. CsA is approved for the treatment of severe atopic dermatitis in adults (Griffiths et al. 2006; Mrowietz et al. 2009; Granlund et al. 1996).

9.1 Safety

On the one hand, the clinical use of cyclosporine is limited due to a wide range of side effects, including irreversible nephrotoxicity after long-term therapy and an increased risk of lymphoproliferative neoplasia, an observation made in a population consisting of organ transplantation

recipients. On the other hand, an investigation with over 1200 psoriasis patients receiving low-dose CsA did show an increased risk for non-melanoma skin cancer but failed to prove an increased risk for lymphoma.

Hand eczema patients being treated with CsA should be closely monitored. The following parameters should be determined before commencing CsA treatment (Mrowietz et al. 2009):

- History of organ dysfunction (especially renal insufficiency) and neoplasia.
- Physical examination including skin examination and blood pressure measurement. Ongoing infections should be excluded.
- Laboratorial parameters including blood count, electrolytes, liver parameters, serum creatinine, urea, urinalysis uric acid, cholesterol, and triglycerides.

10 Methotrexate

Methotrexate (MTX) is an agent used not only to treat several forms of cancer such as acute lymphocytic leukemia or lymphoma but also chronic inflammatory disorders including psoriasis, rheumatoid arthritis, and ulcerative colitis. MTX has been used in medicine for over 50 years now and is considered a drug with favorable risk-benefit profile. The off-label treatment with MTX presents an additional option for the treatment of severely affected hand eczema patients.

11 Clinical Pharmacology

Methotrexate is a weak bicarboxylic acid which presents similar structure to folic acid.

Although intravenous or intramuscular administration of MTX is well documented, dermatological patients are usually treated through oral or subcutaneous route. After oral administration, the drug is rapidly but incompletely absorbed, mostly in the small intestine. MTX uptake is mediated by a saturable transporter, reduced folate carrier 1 (RFC1). Food does not seem to influence the bioavailability of MTX; for this reason the drug may be taken regardless of meals. The interindividual variability of the absorption of oral MTX is reportedly high; usually a value of about 70% is described. Treatment with oral MTX is indeed considered more comfortable, but it is frequently associated with gastrointestinal side effects. Hence, oral administration of MTX should be avoided in patients presenting with gastrointestinal symptoms. Moreover, there is evidence that the subcutaneous administration of the drug results in increased bioavailability, as it bypasses gastrointestinal transport. Patients should be therefore informed of the advantages of the subcutaneous route. MTX is mainly excreted by the kidney as intact drug regardless of the route of administration (Longo-Sorbello and Bertino 2001).

12 Mechanism of Action

The mechanism of action of MTX has not been fully elucidated. MTX inhibits dihydrofolate reductase, leading to inhibition of purine and pyrimidine synthesis which in turn reduces cell proliferation. After entering the cell, polyglutamyl groups are added to the molecular structure of MTX by the enzyme folylpolyglutamate synthase. The formation of MTX polyglutamates inhibits another subset of enzymes responsible for the de novo synthesis of purines. This multifactorial inhibition of DNA replication is thought to inhibit cell proliferation. One fundamental study indicates that MTX is able to induce apoptosis in activated but not in resting lymphocytes, indicating therefore that MTX treatment has not only an antiproliferative effect but also induces immunosuppression probably through a mechanism mediated by T cells. Furthermore, MTX seems to have an anti-inflammatory effect mediated through the accumulation of extracellular adenosine, leading to activation of adenosine receptors which results in apoptosis of activated T cells (Longo-Sorbello and Bertino 2001; Morabito et al. 1998).

13 Efficacy

Although not licensed for the treatment of hand eczema, several studies have shown that MTX could be effective in the treatment of moderate-to-severe adult atopic dermatitis. Of note, one open-label study could show a reduction of 52% in disease activity from baseline (Weatherhead et al. 2007). One more recent study presented similar results (Lyakhovitsky et al. 2010). Both studies report that MTX was well tolerated by atopic dermatitis patients. Moreover, one small study showed positive effects in patients with podopompholyx. Taken together, these data support the concept that MTX, with its antiproliferative and immunosuppressive effect, is an interesting alternative for the treatment of patients with refractory hand eczema.

14 Safety

Although low-dose MTX is usually well tolerated, serious adverse effects have been well documented. These include hepatotoxicity, myelotoxicity, and gastrointestinal abnormalities. On the one hand, there is evidence that folic acid supplementation could reduce these manifestations; on the other hand, recent data suggest that folic acid reduces MTX efficacy for the treatment of psoriasis (Longo-Sorbello and Bertino 2001).

15 Future Perspectives

During recent years, we have witnessed dramatic improvement of the management of patients suffering from chronic inflammatory skin diseases. In particular, the landscape of treatment options for psoriasis patients significantly widened. More recently, studies in atopic dermatitis patients demonstrating the efficacy of the neutralizing IL-4R antibody dupilumab as well as studies investigating the efficacy of Janus kinase (JAK) inhibitors hold promise for new avenues to interfere with the pathogenesis of chronic hand eczema (Levy et al. 2015; Simpson et al. 2016).

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