International Immunopharmacology 53 (2017) 133–142

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Current and future treatment options for pemphigus: Is it time to move towards more effective treatments?

Soheil Tavakolpour

Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
Pemphigus
Autoimmune disease
Treatment
Rituximab
Intravenous immunoglobulin
Personalized medicine

ABSTRACT

Systemic administration of corticosteroid (CS) remains the standard gold treatment for pemphigus. However, because of several long-term adverse effects, steroid-sparing agents are usually prescribed in combination with CSs. Despite the high number of available studies, the choice of best drugs to treat pemphigus remains controversial. Therapeutic approaches for pemphigus can be divided into traditional treatment and emerging ones. Personalized medicine, which aims to increase the efficacy as well as reduce adverse effects of treatments, could be considered as the future option. Here, the most common agents, including azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclophosphamide (CP), rituximab (RTX) and intravenous immunoglobulin (IVIg) have been discussed in detail and compared. Besides, the efficacy and safety profiles of the less frequently used agents such as cyclosporine, dapsone, mizoribine, chlorambucil, plasmapheresis, immunoadsorption and hematopoietic stem cell transplantation have been evaluated. Moreover, some emerging therapeutic options for pemphigus patients, such as B cell activating factor (BAFF), proliferation-inducing ligand (APRIL) inhibitors, anti-cytokine therapy, co-stimulatory and co-inhibitors manipulators and inhibitors of pathogenic signaling pathways (e.g., p38MAPK, c-Myc and EGFR) have been described. In addition to the conventional approaches, some clues to moving towards personalized medicine for the treatment of pemphigus have been proposed. According to the last evidence, seven available first-line combination therapies, including RTX + IVIg, CS + RTX, CS + MMF, CS + AZA, CS + MTX, CS + CP and CS + IVIg were suggested and compared. Subsequently, the most optimum drugs for three different conditions, including patients with no pregnancy or infection, those at high risk of development/reactivation of infection or pregnant women were suggested.

1. Introduction

Pemphigus is categorized under autoimmune bullous diseases, which leads to blisters and erosion on the epithelium of mucous membranes and skin. In pemphigus, immunoglobulin G (IgG) autoantibodies are characteristically directed against desmoglein (Dsg)1 and Dsg3 resulting in acantholysis (loss of adhesion between keratinocytes). This group of rare autoimmune diseases may be fatal if left untreated. Pemphigus can be classified into three major forms, including pemphigus vulgaris (PV), pemphigus foliaceus (PF) and paraneoplastic pemphigus (PNP). However, PV and PF are the two most common forms. Unlike several other diseases, the goal of treatment in pemphigus is not a complete recovery, but inducing a remission or even improvement of lesions and preventing recurrences can be considered as a successful treatment. Moreover, limiting the drug-related side effects and improving the quality of life of patients should be considered during the treatment.

Systemic corticosteroids (CSs) are classically considered as the first-line therapy in pemphigus. These agents are potent inhibitors of NF-κB activation and multiple cytokines. CSs could also act through effects on leukocyte movement, leukocyte function and humoral factors. Moreover, topical forms of CSs are widely used for the treatment of mild pemphigus. However, high cumulative steroid dose is associated with different complications, such as osteoporosis, adrenal suppression, hyperglycemia, dyslipidemia, cardiovascular disease, etc. [1]. Thus, the primary goal of treatment of pemphigus should be inducing remission of disease with the lowest possible cumulative steroid dose. Thus, some immunosuppressive therapies, including, azathioprine (AZA), mycophenolate mofetil (MMF), methotrexate (MTX), cyclophosphamide (CP), cyclosporine and dapsone could be employed as steroid-sparing agents. These drugs act through different signaling pathways, which result in suppression of aberrant immune responses against autoantigens, such as inhibiting the metabolism of purine, interfering with cellular metabolism and mitosis, and exerting anti-inflammatory effects (reviewed in [2]). There are also some other treatment options for non-responders or those who complain of severe adverse effects, including

E-mail address: soheil.tavakolpour@gmail.com.

http://dx.doi.org/10.1016/j.intimp.2017.10.027
Received 16 August 2017; Received in revised form 18 October 2017; Accepted 20 October 2017

plasmapheresis/immunoadsorption, intravenous immunoglobulin (IVIg) and rituximab (RTX). Depending on the limitation of patients and response to treatment, some additional supportive treatments such as intralesional injections of CSs (e.g., triamcinolone acetonide) may be beneficial in the management of pemphigus patients [3].

Despite the several reports associated with efficacy/safety of conventional and newly emerged drugs for pemphigus, choosing optimum dose and also type of treatments in a different phase of this disease has remained a debatable issue. In fact, selecting the proper drugs with high efficacy and low side effects is strongly influenced by other factors, including presence of other diseases (e.g., infection), enzyme activity (e.g., thiopurine methyltransferase [TPMT]), pregnancy, accessibility to drugs, and also cost. Additionally, it is expected that a wide range of genetic and immunological variations be involved in drug response and control of side effects. This concept is known as personalized medicine, which suggests particular treatment options as well as the optimum drug dose, based on the genetic profile of patients. Unfortunately, there is no study associated with personalized medicine for pemphigus. Here, the best treatment strategies for pemphigus patients with different conditions (e.g., non-responders to conventional treatments, pregnant women with pemphigus, or those at risk of infections), and also efficacy and reported side effects of current therapies had been reviewed. Furthermore, emerging future treatments, and approaches to implement personalized medicine were also discussed.

2. Common treatment options

2.1. Systemic corticosteroids

Since the discovery of glucocorticoids in the 1940s, they have become one of the most widely and efficient agents for the control of inflammatory and autoimmune diseases. These compounds exert their anti-inflammatory, immunosuppressive, antiproliferative and vasoconstrictive effects by influencing multiple signal transduction pathways [4]. For example, they modulate gene expression and lead to switching off or switching several activated inflammatory or anti-inflammatory genes, respectively [5]. Although, adjuvant agents could be used at the time of diagnosis, systemic CS therapy is usually considered as the primary and first-line treatment in pemphigus [6]. However, available reports related to this type of therapy show the high efficacy, but severe side effects [7,8]. European Dermatology Forumin Cooperation with the European Academy of Dermatology and Venereology, recommended commencing prednisone/prednisolone as the first-line treatments at the initial dose of 0.5 to 1.5 mg/kg daily, in which, the dose can be tapered by 25% in biweekly steps to reach 20 mg/day and then tapered slowly [3]. It is expected that patients respond to this therapy within a maximum of two weeks [3]. For cases with more severity or those without response to given dose, prednisone/prednisolone could be given at a higher dose, about 1 to 3 mg/kg daily [6]. In some guidelines, it was recommended that starting with full steroid dose could lead to a more favorable outcome, even in less severe cases [9]. However, not all the studies had confirmed this idea. If due to highly active, widespread form of the disease and/or resistance to conventional oral steroid therapy, high doses are required (e.g., > 100 mg/day prednisone equivalent), pulse treatment with either oral or intravenous steroids may be considered [10–12].

2.2. Mycophenolate mofetil (MMF)

MMF is the prodrug of mycophenolic acid (MPA), produced by *Penicillium brevicompactum* more than a century ago. MPA can impair the immune responses through several signaling pathways, such as inhibiting the DNA synthesis by selectively inhibiting inosine monophosphate dehydrogenase, and depleting the guanosine nucleotides preferentially in T and B cells throughout the blocking cell cycle in the G1 phase, and results in inhibition of lymphocyte proliferation [13,14]. Together, these could cause suppression of both cellular and humoral immunity. MMF is increasingly being used as an adjuvant therapy in PV and PF and was recommended as a first-line steroid-sparing agent in PV patients [15]. It was suggested that MMF should be started at a low dose (500 mg/day) and weekly raised dose of 500 mg/day until the final dose of 2 g/day for better gastrointestinal tolerance [3]. Although, both AZA and MMF have been reported to be equally effective with regards to treatment response in pemphigus [16], because of less liver toxicity profile of MMF, it seems to be a more attractive choice [17,18]. Doukaki et al. [19] studied a total of 222 patients with pemphigus (201 PV patients and 21 PF patients), who were treated with MMF. As a result, a high number of patients (78.8%) showed clinical improvement of the disease, but within a broad range of time, and it was reported that the adverse events were dose-dependent. In another study, low dose of MMF (1 g/day) was suggested as an effective dose with no serious undesired side effects [20]. Due to the fact that MMF was found to be a non-mutagenic agent (in contrast to AZA), it may be superior to AZA in the treatment of pemphigus [16].

Sometimes, combination therapy with systemic CSs and MMF at high dose (e.g., 3 g/day) may not offer any advantage over monotherapy treatment with systemic CSs in pemphigus patients [21]. In a study, MMF did not show a benefit on the primary endpoint, but it had a significant impact on hastening the average time for disease control in addition to delaying the time to relapse [22]. Although, no neoplasm developed during the follow-up period in pemphigus patients under MMF therapy [23], there is a risk of malignancy in humans, which is thought to be related to duration and intensity of immunosuppression [24]. Additionally, because it could be problematic for a female in child-bearing age and even men, it may not be recommended for expectant mothers [25].

2.3. Azathioprine (AZA)

AZA is a prodrug which could rapidly be converted to 6-mercaptopurine after absorption. AZA exerts its suppressive effects primarily through inhibition of DNA and RNA synthesis, also suppressing the de novo pathway of purine synthesis. Besides, induction of apoptosis and blockade of TCR-induced or costimulatory signals are other suggested underlying mechanism of actions [26]. AZA, an effective corticosteroid-sparing therapy is a well-established choice as an adjuvant drug for treatment of pemphigus [27]. Firstly, it was introduced as an effective treatment for pemphigus more than four decades ago [28]. Subsequently, numerous studies had reported its high efficacy because of its steroid-sparing effect, reduction of mortality and high rate of remission in patients with pemphigus [29–31]. Similar to the MMF, it was recommended as a second-line treatment in refractory pemphigus patients or cases of contraindications to CSs. AZA was recommended to be started at the dose of 50 mg/day, which could be increased to 2.5 and 1.5 mg/kg/day for those with high or intermediate/low TPMT activity, respectively [3]. Although, the dose of AZA is closely related to TPMT activity, in general, it was recommended that it should be started at a dose of 1 to 3 mg/kg daily [32]. TPMT activity measurement before starting AZA could also be a promising approach for probable toxic effect and suboptimal doses of the drug. Over the recent years, emerging results suggest that AZA be replaced by MMF, which is a less toxic and non-mutagenic adjuvant with the same efficacy and corticosteroid-sparing effects [16]. Regarding the increasing cancer risk as a result of AZA therapy, there are controversial results [33–35]. However, monitoring of AZA-exposed patients for malignancy is strongly recommended. Additionally, because of the risk of congenital abnormalities, AZA should be avoided in pregnancy [25].

2.4. Methotrexate

MTX is an antimetabolite drug, which was first synthesized for treatment of leukemia several decades ago [36]. MTX reversibly