SYMPTOMATIC TREATMENT

AVAILABLE TREATMENT OPTIONS UPDATE AND REVIEW OF LITERATURE

Classification of literature on evidence level regarding treatment with corticosteroids and other symptomatic treatments are shown in the supplementary files 3 and 4 respectively.

1.- Topical steroids: There are two main studies that analyze the treatment of DRESS with topical steroids vs systemic corticosteroids, the study by Um SJ et al [1] and the study by Funck-Brentano et al [2]. Um et al designed a prospective study in which all patients with DRESS were initially treated with topical corticosteroids and antihistamines for 5-7 days and if there was evidence of internal organ involvement and persistent or aggravating clinical findings during the initial 5 to 7 days, they administered prednisolone 1mg/kg [1]. They included 38 patients; 58% of patients were treated with topical corticosteroids and antihistamines (no systemic corticosteroid) with complete recovery.

In the retrospective non-blinded study of 38 cases performed by Funck-Brentano et al [2], treatment with topical steroids alone (clobetasol propionate (30g/d) or betamethasone dipropionate (45g/d)) was prescribed to 25 patients with DRESS-related skin disorders in the absence of life-threatening organ involvement but some of them with mild visceral involvement. Complications of DRESS were less frequent with topical steroids than with systemic steroids [1,2]. The authors concluded that systemic steroids may not be required for the management of mild forms of DRESS, and may be reserved for more severe cases [2].

High or super high potency topical corticosteroid treatment is recommended by experts [3, 4, 5], in mild cases and DRESS cases without severe organ involvement, this is with no evidence of pulmonary or renal involvement and only modest elevation of liver transaminases (ie <3 times ULN) [6] (LE:3 GR:D). This treatment can be associated to antihistamines and emollients [4].(LE:3 GR:D).

2.- Systemic corticosteroids. For many years, the treatment of DRESS has been based on the use of oral systemic corticosteroids (dose equal 0.5- 2 mg/kg /day of prednisone or equivalent) with an important improvement of symptoms and laboratory parameters, within several days after the start of treatment [3, 7, 8].

Despite that systemic corticosteroids are accepted as the standard treatment, the efficacy and benefits of this treatment have not been formally studied in randomized placebo-controlled trials [7, 9] and there is a lack of guidance on optimum dosage regimens. These trials are difficult to perform due to the life threatening nature of this syndrome [3].

Natkunarajah et al conducted a prospective study with 10 patients to determine the efficacy of pulsed intravenous methylprednisolone 30mg/kg for 3 days followed by a short reducing course of oral prednisolone [10]. They concluded that an aggressive corticosteroid regimen is associated with good clinical outcome and acceptable tolerance [10]**.** The same good outcome was observed by Kocaoglu in 2 pediatric patients [11]. It has been suggested that pulsed intravenous corticosteroids may be beneficial in cases with significant visceral involvement or when there is no improvement or with exacerbation of symptoms with oral corticosteroids [3,7,10,11,12 13].

Different advantages and disadvantages of treatment with systemic corticosteroids have been revealed from different studies. The well known secondary adverse effects of corticosteroids mainly at high and prolonged doses are among the disadvantages of treatment with systemic corticosteroids [8,10]. Other disadvantages are relapses or flare ups of the disease when tapering doses [2], reaching 18.5% flare ups in the series of Wongkitisophon [8]. Viral reactivations [2], [14], CMV disease and HHV-6 associated clinical symptoms [15], infections like pneumonia and sepsis [2], as well as opportunistic infections [1] have been more often found in the series of patients treated with systemic corticosteroids than in those not treated with them [1,2,14].

On the other hand, in the retrospective study published by Ushigome et al [14] in the non-systemic corticosteroid treatment group 2/20 developed autoimmune complications (lupus erythematosus and autoimmune thyroiditis) and 44% developed autoantibodies in the period over 6 months following the disease [14]. It has been suggested by Shiohara et al [16] that systemic corticosteroids may not only lessen a variety of clinical symptoms at the acute stage but also by restoring the impaired Treg activity, preventing the generation of autoimmune responses occurring at the resolution stage and preventing autoimmune sequelae [16].

The questions of whether all DRESS patients should initially receive systemic corticosteroids at which dose and for how long remain to be determined [17]].

Systemic corticosteroids should have their dose reduced, after the clinical and laboratory control of the disease. It should be done slowly even upon rapid resolution of clinical manifestations [17] to prevent abrupt deterioration and recurrence of the symptoms of the disease [3,7,18]. Recommended time of tapering is variable

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depending on the experts, over 6-8 weeks [3,17-19], 8-12 weeks [6], 3-6 months [12]. Flare-ups during corticosteroids withdrawal are managed successfully by increasing dose followed by slower taper [13].

Patients with DRESS are at greater risk of subsequently developing the wide spectrum of immune reconstitution syndrome (IRS) ranging from cytomegalovirus (CMV) disease to autoimmune disease [18] and the use of systemic corticosteroids represents an important factor that increases the risk of disease progression to full manifestations of IRS upon the withdrawal or reductions. HHV- 6 and CMV viral loads were found significantly higher in patients with DRESS receiving systemic corticosteroids compared with those without corticosteroid therapy. Moreover the mean duration of CMV and HHV-6 reactivations was also longer in the steroid treated group [15]. This effect of corticosteroids on viral reactivations is likely to be an unanticipated consequence of a tapering corticosteroid dose [20].

Asano et al [20], observed that the increase in CMV viral loads in one patient coincided with a tapering of corticosteroid dose. Asano et al found that older and male patients with antecedents of high human herpesvirus 6 DNA loads were at risk for CMV disease irrespective of corticosteroid administration. A rapid reduction in white blood cell numbers was also predictive of the onset of CMV disease [20]. Given the high risk of sequelae from CMV reactivation in patients with DRESS, the direct anti-CMV medications with a gradual reducing dose of corticosteroids may help to avoid disease progression to full manifestations of IRS [20].

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Physicians should pay attention to a proper balance between the needs of corticosteroids for relief of symptoms and the clinical signs and the possible disadvantages of its prescription.

The use of systemic corticosteroids for the treatment of DRESS with severe organ involvement has not been evaluated in randomized trials. However, there is a general consensus among experts about its use at high dose in DRESS with severe organ involvement) [3,4,5,13,18], particularly in patients with renal and/or pulmonary injury [6].

2a. Liver injury and corticosteroid treatment

Systemic corticosteroids are often used in drug-induced hepatitis but their benefits are still not fully proven [21].

In the systematic review performed by Cacoub et al, on DRESS cases reported in literature (1997-2009), 9 cases resulted in death (5%), almost all of these cases were associated with liver involvement and treatment with corticosteroids did not prevent a fatal outcome [22]. Other cases in which treatment with corticosteroids at high doses did not prevent liver transplant have been reported [23, 24].

In the retrospective study or 29 patients with DRESS by Lee T et al [25] the use of systemic corticosteroids did not significantly affect either recovery from liver injury or mortality.

Nevertheless in the single center retrospective study by Hu et al in 203 patients with severe DILI (total bilirubin >5mg/dL), treatment with corticosteroids not only decreased mortality but also shortened the time duration to recovery [26](LE: 2+,

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GR:C). A higher rate of disease resolution and a shorter time for recovery was also observed in the retrospective series of 300 cases by Hou et al [27] (LE:2+, GR:C). However, the efficacy of corticosteroids for drug induced liver injury (DILI) has still not been clearly elucidated to date and it is not routinely recommended for this condition. Prompt withdrawal of the suspected drug usually results in a 50% decrease in serum ALT within 8 days of discontinuation [28]. Hu et al routinely wait for about a week to see if there are any changes in the liver biochemistries after drug withdrawal in mild to moderate DILI (26)(Hu PF, J Dig Dis 2016). If there is no improvement or the condition gets even worse the use of corticosteroids is considered [26]. Nevertheless corticosteroids were not efficacious in treatment of cases with severe acute liver injury or acute liver failure[26,29] . (LE: 2+, GR:C)

2b.Kidney injury and corticosteroid treatment

Corticosteroids are frequently used on the basis of several observational studies that showed a greater and faster recovery of kidney function in patients who received them [30-32]. Early initiation of corticosteroids (within 15 days of diagnosis) has been associated with better outcome and complete functional renal recovery in these two large multicenter retrospective studies with biopsy-proven cases of drug-induced acute interstitial nephritis (DI-AIN) [31,33].

There is a general consensus among experts on the use of systemic corticosteroids in patients with DRESS and renal involvement [4, 6]. The optimal dose and duration of therapy are unclear. One approach is to administer prednisone 0.5 to 2 mg/kg per day until clinical improvement and normalization of the laboratory parameters are obtained and then tapered over the ensuing 8 to 12 weeks [6].

In the study by Fernández-Juarez including 182 patients with biopsy-proven cases of

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DI-AIN from 13 centers in Spain [33] the initial dose of prednisone used was around 0.8 mg/kg per day. The maintenance of this maximum initial dose beyond 3 weeks did not seem to confer greater probability of kidney function recovery and also suggested that extending total corticosteroid treatment beyond 8 weeks does not ensure a better outcome; on the contrary, it might increase the risk of treatment complications [33].

Another regimen commonly used in drug-induced acute interstitial nephritis is a "pulse" methylprednisolone (250-500mg intravenous injection) for 3 to 4 days followed by oral prednisone 1mg/kg/d and progressive tapering over 8-12weeks after the serum creatinine has returned to or near baseline level [28, 31]. However in recent studies no significant differences were found regarding time and extent of kidney function recovery between patients who received steroid pulses and those who did not [33, 34]. This finding was consistent with a recently published randomized controlled trial that showed an equal effectiveness of oral and pulse steroids in achieving remission at 3 months post-biopsy in 29 cases of DI-AIN [35].

All these treatments should be performed under the supervision of appropriate specialist.

3. Other therapies.- Other therapeutic approaches have also been tried in DRESS patients, in single case reports and small case series. The most important ones are detailed below.

3.1 Intravenous IgG (IVIG). It is a pooled purified human immunoglobulins, composed mostly of immunoglobulin G. High doses of IVIG have some important immunological effects that can justify its use in DRESS treatment. It compensates for the decrease in concentration of immunoglobulins detected in the patient's blood and

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the defects of the immune protection against HHV-6; moreover high doses of IVIG have an anti-inflammatory effect that can regulate the immune response, as seen in the treatment of autoimmune diseases [36]. In addition IVIG may control B and T cell proliferation and subsequently block the production of interleukin 5 (IL-5) and eosinophil maturation [37].

Several cases have been reported either successfully [36,38-42], or unsuccessfully treated with IVIG (2 over 3 patients in a series of 15 severe cases) [38]. Dosage can vary from 0.4g/kg to 2g/kg [4,36,43] for 2-5 days. It has also been used in a monthly regimen for 8 months as a corticosteroid sparing agent [43] and as monotherapy [36, 44] or associated to N-acetyl cysteine [39] or to systemic corticosteroids [40, 42,45] . However, a prospective study of 6 patients with severe DRESS syndrome did not support a beneficial effect of IVIG [44]; 5 of 6 patients experienced severe adverse effects (2 severe malaise, 1 hypertension, 1 hypotension, 1 pulmonary embolism) and 4 patients had to be treated with oral corticosteroids because of the adverse effects of IVIG or uncontrolled DRESS syndrome. Consequently, the authors did not recommend the use of IVIG monotherapy in the treatment of DRESS syndrome [44]. Kano et al suggest that differences in the outcome could be dependent in part on functional capabilities of anti-virus IgG contained in IVIG [45].

Marcus N et al [46] recently reported a series of 7 paediatric patients with severe DRESS syndrome, successfully treated with IVIG in addition to systemic corticosteroids, with no mortality. They used an IVIG dose of 2g/kg in 6 patients and 1g/kg in one patient, and obtained a fast improvement within the first 24-48 hours [46].

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The group of drug reactions of the French Society of Dermatology published in 2010 the results of a consensus of experts on the therapeutic management of DRESS and recommend corticosteroids associated with IVIG at a dose of 2g/kg over five days in cases of DRESS with life-threatening signs. They recommend that IVIG should not be used without associated steroids [4]. This recommendation has also been included by Hussain in his review [12]. However other experts as Mockenhaput in her review in Uptodate [6] do not suggest the use of IVIG in DRESS while awaiting further evidence.

3.2 Cyclosporine (CsA) is a potent immunosuppressive agent. The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent T-lymphocytes. Because cyclosporine targets T cells specifically, by downregulating activation of nuclear factor of activated T cells, it might be an appropriate medication to use in the treatment of this condition [18]. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2. There is a scarce number of reported cases of DRESS treated with cyclosporine [47-54]. The dosage used was 4-5mg/kg/d from 3 to 7 days. It was also used as a sparing corticosteroid agent [50]. A successful response in most of the reported cases of DRESS syndrome treated with cyclosporine was observed [48,50,51]. Kirchhof et al suggest it could be considered as first-line therapy, particularly in patients with concerns about using long courses of systemic corticosteroids [48]. There are also 2 cases of overlap SJS/TEN and DRESS due to benznidazole treated with oral corticosteroids and cyclosporine with success [55].

Experts´ systematic reviews point out cyclosporine as other potential therapies [12,13]. This treatment does not appear in the guideline elaborated by the consensus of

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experts on the therapeutic management of DRESS of the French Society of Dermatology in 2010 [4].

Roujeau and Mockenhaupt in Uptodate 2018 and 2019 [6] include cyclosporine in the management recommendations for DRESS. Although evidence is limited, the authors recommend cyclosporine as a second-line therapy for patients with DRESS and severe organ involvement who do not respond to systemic corticosteroids and for patients in whom corticosteroids are contraindicated [6].

3.3 Cyclophosphamide. Few case reports support the efficacy of this drug in DRESS syndrome treatment [56,57]**.**

3.4 Plasmapheresis. There are few case reports showing the efficacy of this treatment. [49, 58, 59]. Plasmapheresis is considered a treatment option if symptoms deteriorate despite corticosteroid therapy [19], especially in DRESS with multiple organ injury [58].

3.5 Anti-herpesvirus drugs, such as valganciclovir, ganciclovir, cidofovir and foscarnet may be helpful in preventing or minimizing complications related to HHV-6 and CMV reactivations [20, 60].

Although there are no studies evaluating the treatment of DRESS with antiviral agents, merely case reports [20, 60], some experts recommend treatment with antiviral agents in addition to steroids and/or IVIG in cases with signs of severity with confirmation of major viral reactivation [12, 4, 13]. Other experts recommend that antiviral agents may be warranted for patients with DRESS if virus reactivation is demonstrated and suspected of contributing to severe complications (eg. encephalitis, severe erosive colitis, hemophagocytosis) [6]. Given the substantial toxicity of the available antiviral agents and the natural course of spontaneous resolution, they do

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not recommend this treatment routinely [6]. There are no references as for dosage and duration of treatment. Moling et al reported a DRESS case treated with oral valganciclovir at 900mg/12h and then 450mg/12h for 3 months [60]. Asano reported two cases treated with IVIG, corticosteroids and ganciclovir at dose of 20mg/d [20].

Mizukawa Y et al developed a scoring system (taking into account age and other clinical variables) that may be useful for predicting CMV-related complications and early intervention with anti-CMV agents should be considered in patients with scores ≥4 and/or evidence of CMV reactivation [61]. Antiviral drugs have toxic effects and their benefits need to be evaluated in clinical trials [38]. The introduction of drugs that are safer and more effective, particularly against HHV-6, will probably expand the indications for antiviral therapy [5].

3.6. N-acetylcysteine. This agent has been proposed in DRESS treatment, mostly in anticonvulsant-induced DRESS syndrome, because it might neutralize the culprit drug-derived reactive metabolites [9].

N-acetylcysteine use has been suggested in combination with IVIG [39] and also combining prednisone and valganciclovir [60]. A randomized controlled trial in pediatric population suggested worse outcome in treatment with N-acetylcysteine in cases with acute liver failure [62]. Nevertheless in adult population a double-blind trial showed that intravenous N-acetylcysteine improved transplant-free survival in patients with early stage non-acetaminophen-related acute liver failure [63].

3.7.-Mepolizumab: An anti-IL5 mAb shows promise as a novel therapy in the treatment of relapsing/refractory DRESS. Recently a DRESS case treated with

Mepolizumab (100mg/monthly for 3 months) as a steroid sparing agent has been published [64].

A potential drug development for therapeutics and an international collaboration of clinical trials for DRESS treatment is still necessary.

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