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Treatments and supportive therapies for oral manifestations of chronic graft-versus-host disease

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ABSTRACT. The aim of this study was to conduct a systematic review of treatments and therapies for oral manifestations of chronic graft-versus-host disease, aiming at improving patients' quality of life and mainly the reduction of mortality caused by graft-versus-host disease. A systematic review was carried out by two evaluators, a Dentistry professor and an undergraduate student. A selection of open-access full-text online articles, carried out on PubMed, GoPubmed, NLM Gateway, LILACS, BIREME, SciELO, IBECS, and Web of Science. The survey was completed in July 2012. Of the 1147 studies found, 52 fit the selection criteria. Patients (n = 2130) received different treatment regimens, either systemic or topical. Drugs for systemic therapy were divided into those with action on the inhibition of proliferation and/or release of T and B cells, with action on inflammatory disorders, and of immunomodulatory effect. Topical drugs were divided into their pattern of mucosal absorption and their ability to act on tissue growth factors. The analysis of articles concluded that the most used systemic drugs were Methylprednisolone and corticosteroids, and Tacrolimus and topical Cyclosporine for topical and local therapy.

Keywords: bone marrow transplantation. graft-vs-host disease.

Tratamentos e terapias de suporte para manifestações orais da doença crônica do enxerto contra hospedeiro

RESUMO. O objetivo do trabalho foi realizar uma revisão sistemática sobre tratamentos e terapias de suporte para manifestações orais da doença crônica do enxerto contra hospedeiro, visando à melhoria da qualidade de vida dos pacientes e, principalmente, a redução da mortalidade causada pela doença do enxerto contra hospedeiro. A revisão sistemática foi realizada por dois examinadores, um professor e um graduando de odontologia. A seleção de acesso aberto de artigos online de texto completo, realizadas no PubMed, GoPubmed, NLM Gateway, LILACS, BIREME, SciELO, IBECS e Web of Service. A revisão foi concluída em julho de 2012. Dos 1.147 estudos encontrados, 52 se enquadraram nos critérios de seleção. Os pacientes (n = 2130) receberam diferentes tratamentos, seja de forma sistêmica ou tópica. Os medicamentos para tratamento sistêmico foram divididos entre aqueles com ação na inibição da proliferação e / ou liberação de células T e B, com ação em doenças inflamatórias, e de efeito imunomodulador. Drogas tópicas foram divididas em seu padrão de absorção da mucosa e a sua capacidade para atuar sobre os fatores de crescimento de tecidos. A análise dos artigos permitiu concluir que os medicamentos sistêmicos mais utilizados foram Metilprednisolona e corticosteróides, e Tacrolimus e Ciclosporina tópica para a terapia tópica e local.

Palavras-chave: transplante de medula óssea. doença enxerto-hospedeiro.

Introduction

Within all organ transplants, bone marrow transplantation (BMT) has increased worldwide in the past 40 years (Silva, Bouzas, & Filgueira, 2005). According to the Brazilian National Institute of Cancer, about 2000 transplants are done in the country, a number that may increase 30% every year.

However, some complications can occur after the procedure, such as chronic graft-versus-host disease (GVHD), common in 50-80% of all BMT. GVHD is the main responsible transplant-related morbidity and mortality, accounting for nearly a quarter of all deaths (Chao, 1998).

Oral manifestations of GVHD may occur in 30-80% of the cases (García; Molina; González, 2006), and can be classified as (a) mild, when the oral mucosa presents leukoedema, white streaks, burning sensation of the mouth and xerostomia; (b) moderate, with the mucosa showing maculopapular

rash, microstomia, painful ulcerations and mucoceles, and (c) severe, with bullous lesions (Chao, 1998). Oral signs of the disease can be one of the earliest manifestations of systemic GVHD, reason why dentists should be members of the multiprofessional approach to treatment of the disease. They should be able to diagnose such signs and refer patients to oncologists as soon as possible, so that patients receive an early medical and dental treatment and may have a better prognosis.

Aiming at performing an analysis of existing therapies treatments and supportive treatments for oral manifestations of GVHD, this paper presents a systematic literature review of treatments and therapies on the disease.

Material and methods

The systematic review was carried out by two evaluators, a Dentistry professor and an undergraduate student, who run two independent web-based searches on the following online database: Pubmed, GoPubmed, NLM Gateway, LILACS, BIREME, SciELO, IBECS, and Web of Science. The articles should be in English and have abstracts. The first search combined the Medical Subject Headings (MeSH) terms 'Graft versus host disease' and 'Oral cavity'. The second search used the terms 'Cyclosporine' or 'Clofazimine' or 'Steroids' or 'Hydroxychloroquine' or 'Methotrexate' or 'Mycophenolate mofetil' or 'Eicosapentaenoic acid' or 'Pentostatin' or 'Rituximab' or 'Sirolimus' or 'Tacrolimus' or 'Thalidomide' or 'Budesonide' or 'Extracorporeal' or 'Platelet' or 'Azathioprine' and 'Graft versus host disease' and 'Oral cavity'. The descriptor was 'graft versus host disease'. The survey was completed in July 2012.

The online searches resulted in 1147 articles, but during the screening process these texts revealed additional articles, which integrated the sample. The screening process started using the title and the abstracts and was based on (a) inclusion criteria: articles that described different treatments and therapies for chronic GVHD with oral manifestation; open-access full-text online articles, and no age restriction, and (b) exclusion criteria: review articles, case studies, letters to editors, and general news. Once the duplicated and not relevant articles were discarded, the texts were fully analyzed and the eligibility criteria applied: articles with minimal size sample of 5 patients; randomized controlled trials and open-label trials; studies in humans, both adults and children; patients with chronic GVHD; cases of primary outcomes (i.e., no analysis of recurrent GVHD); studies on treatments and supportive therapies for GVHD with systemic, topic, or extracorporeal application, and patients with chronic GVHD with oral manifestation (Figure 1).

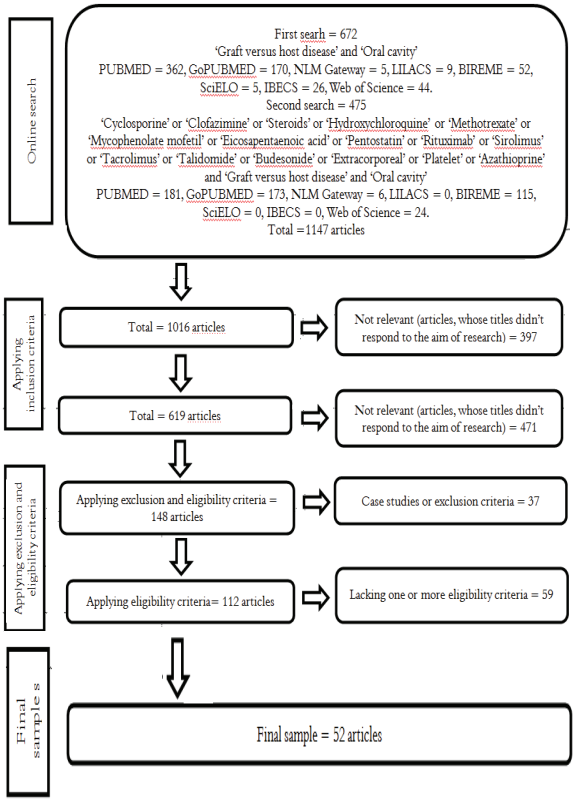

Figure 1. Flowchart with online search and the screening criteria to select the appropriate articles on chronic GVHD with oral manifestation (as adapted from Nabil & Samman, 2012).

Within the 52 selected articles, the information tabulated was: therapeutic agent, study design, number of patients, oral response to treatment, and the drugs' major complications. The 'data were' imported into 'Microsoft Excel spreadsheet' by one of the reviewers, whereas the second double-checked them.

Results

The review showed several systemic therapies for the treatment of chronic GVHD. As the effectiveness of the drugs may vary depending on the targeted organ (Couriel et al., 2006), the review analyzed only those of global action that can influence the oral mucosa.

Three out of the 52 articles were open-label randomized double blind designed, whereas the remaining 49 were open-label single-arm. Response to treatment is reported as complete,

when treatment led to the cure of the disease, or partial, when signs and symptoms in an organ or part of the body disappeared due to treatment.

Systemic Therapy

The drugs were divided into three types:

(a) Those with action on the inhibition of proliferation and/or release of T and B cells: Cyclosporine, Hydroxychloroquine, Sirolimus, Tacrolimus, Pentostatin, Rituximab;

(b) Those with action on inflammatory disorders: Clofazimine, Methotrexate, Methylprednisolone, Thalidomide;

(c) Drugs of immunomodulatory effect: Mycophenolate mofetil, Extracorporeal photopheresis.

Drugs with action on the inhibition of proliferation and/or release of T and B cells

These were the most examined systemic drugs among the 52 studies, found in 15 articles (Table 1).

Drugs with action on inflammatory disorders

The effect of drugs on inflammatory disorders in the treatment of GVHD was investigated by seven studies (Table 2).

Drugs of immunomodulatory effect

Mycophenolate mofetil was the most recently examined drug among those of immunomodulatory effect (Parker et al., 1995; Akpek, Lee, Anders, & Vogelsang, 2001; Dall'Amico & Messina, 2002) (Table 3). It is rapidly absorbed when administered orally and is used for prevention of transplant rejection (Furlong et al., 2009). A study carried out in 2000 (Busca et al., 2000) showed good overall response to treatment (60%), whereas the results of a more recent study, 2009, were not as promising: 59% of patients required additional treatment, and 17% developed gastric toxicity (Furlong et al., 2009).

Table 1. Systemic therapy using drugs with action on the inhibition of proliferation and/or release of T and B cells. OA = Oral administration; IVA = Intravenous administration; n = number of patients. Exp.= Experimental Group.

Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Cyclosporine (OA 6.25 mg Kg^{-1} / 2 X day, or IVA 1.5 mg Kg^{-1} / 2 X day), alternated with Prednisone (CP) (OA 0.5 mg Kg^{-1}) X Cyclosporine + Prednisone + Thalidomide (CPT) (50 mg / 4 X day for adults, 0.75 mg kg^{-1} / 4 X day children) (Arora et al., 2001)	Open label randomized double blind	CP = 27 CPT = 27	Similar responses for both groups Complete response 22/52 Died: CP 10/27 , CPT 9/27	CP improvement 16/27 CPT satisfactory results within 1 year 21/27	CP: hypertension 15/27 CPT: drowsiness 17/27, constipation 15/27
Cyclosporine (OA 6 mg Kg^{-1} / 12/12h) + alternated days with Prednisone (OA 1 mg kg^{-1}) (Sullivan et al., 1998)	Open label single-arm	61	Partial response 20/61 Complete response 17/61 Died 25	Biopsy performed, oral results not reported	Hypertension 13/61 Varicella zoster 16/61 Bacteraemia 12/61 Other severe infections 19/61
Cyclosporine (OA 6 mg Kg^{-1} / 2 X day) + alternated days with Prednisone (CP) (OA 1.0 mg kg^{-1} / day) x Prednisone (P) (Koc et al., 2002)	Open label randomized, double-arm	CP =142 P=145	Survival rate: CP 24/142 , P 18/145	No oral results	Avascular necrosis CP: 18/142 P: 32/145
Hydroxychloroquine (OA 400 mg /2 X day) (Fong et al., 2007)	Randomized double-blind	Exp. 40 Placebo: 35	Inefficient prophylactic and on survival Developed GVHD: Exp 24/40, Placebo 27/35	No oral results	Well tolerated, no associated side effects
Hydroxychloroquine (OA 800 mg/day) (Gilman et al.; 2000)	Open label single-arm	32 (13 Buccal)	Response over 713	General improvement 11/13 Partial or Complete response 5/13	No relevant toxicity
Sirolimus (OA 10 mg, followed by 5 mg daily) (Johnston et al., 2005)	Open label single-arm	19 (13 Buccal)	General response 5/16 Discontinued treatment 9/16 Died 2/16	Partial response 4/6 Complete response 2/6	Renal failure, increase in the serum creatinine levels 4/16 Hemolytic-uremic syndrome 2/16
Sirolimus (OA 2 mg /1 X day) (Jurado et al., 2007)	Open label single-arm	47	Complete response 18/47 Partial response 20/47 Refractory to treatment 6/47 Died 2/47 Discontinued treatment due to toxicity 1/47	Not reported	Renal failure

Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Tacrolimus (OA l 0.12 mg Kg^{-1} /day) (Carnevale-Schianca et al., 2000)	Open label single-arm	39 (22 Buccal)	General response 5/39 Clinically stable 3/39 Discontinued treatment due to toxicity 4/39 Treatment failed 29/39 Died 9/39	Not reported	infections, nephrotoxicity144
Pentostatin (4mg m^{-2}/dosage) (Goldberg et al., 2003)	Open label single-arm	5 (2 Buccal)	Clinical improvement 5/5	Complete response 2/2	Infections, nausea, vomit, fatigue.
Pentostatin (IVA 4 mg m^{-2}/every 2 weeks) (Jacobsohn et al., 2007)	Open label single-arm	58 (39 Buccal)	General response 32/58 Interrupted treatment 2/58 Died 19/58	Symptoms improved 24/39 Symptoms worsened 10/39	Nausea, infections
Pentostatin (IVA 4mg/m^2/ every 2 weeks (Jacobsohn et al., 2009)	Open label single-arm	51 (30 Buccal)	General response 27/51 Discontinued treatment due to toxicity 13/51 Died 4/51 Survival rates increased in 3 years	Complete response 9/30 Partial response 8/30 Lesions stabilized 7/30 Symptoms worsened 6/30	Infection 15/51
Rituximab (not reported) (Zaja et al., 2007)	Open label single-arm	38 (23 Buccal)	General improvement 24/38 Died 8/38	Oral response 10/23 Complete response 4/23	Infections, tremor, renal failure
Rituximab (IVA 100 mg pre-determined days) (Gutiérrez-Aguirre et al., 2012)	Open label single-arm	15 (13 Buccal)	- After 30 days Partial response 10/15 Complete response 5/15 - After 90 days Partial response 7/15 Complete response 4/15 GVHD recurrence 3/15 - After 365 days Patients evaluated 5/15 Partial response 2/5 Complete response 2/5	Not reported	Fever, shivering, infection
Rituximab (IVA 375 mg m^{-2} pre-determined days) (Teshima et al., 2009)	Open label single-arm	7 (5 Buccal)	Partial response 2/7 Died 2/7	General response 1/5	Infections
Rituximab (IVA 375 mg m^{-2} weekly) (Kim et al., 2010)	Open label single-arm	37 (28 Buccal)	Complete response 8/37 Partial response24/37 Response maintained by the end of evaluation 21/37 Interrupted treatment 6/37 Died 9/37	Complete response 4/28 Partial response 16/28	Infections, GVHD relapse

Table 2. Systemic therapy using drugs with action on inflammatory disorders. OA = Oral administration; IVA = Intravenous administration; n = number of patients.

Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Clofazimine (OA 300 mg daily) (Wang et al., 2009)	Open label single-arm	22 (6 Buccal)	Partial response 12/22 Complete response not reported Died 6	Partial response 3/6 Lesions stabilized 1/6	Gastrointestinal effects 8/22 Hyperpigmentation 12/22
Methotrexate (IVA 10 mg or OA 15 mg) (Johnston et al., 2005)	Open label single-arm	86 (12 Buccal)	General improvement 71/86 Better efficacy on: skin 77/86, liver 64/86, mouth 36/86	Improvement 5/12	Cytopenias, mucositis 3/86
Methotrexate (IVA 7.5 mg m^{-2}/ weekly) (Jurado et al., 2007)	Open label single-arm	38 (4 Buccal)	General response 38/38	Complete response 1/4 Partial response 2/4	Hematologic toxicity 7/38

Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Methotrexate (OA or VP7.5 mg m^{-2}/ weekly) (Carnevale-Schianca et al., 2000)	Open label single-arm	21 (9 Buccal)	Reduced Prednisone 10/21 Reduced munodepressant 4/21 Kept dosage 5/21 Increased imunodepressant /21 Interrupted treatment 1/21	Complete response 1/9 Partial response 1/9 Stable 7/9	Developed GVHD in sites previously unaffected 3/21
Methylprednisolone(OA or IVA10 mg kg^{-1} day^{-1}/ 4 days) (Huang et al., 2005)	Open label single-arm	56	More response to treatment 27/56 Less response to treatment 15/56 Interrupted treatment 10/56 Died 6/56	Not reported	No severe side effects Hypertension 2/56 Infections 3/56
Thalidomide(OA adults 200mg, OA children 3 mg kg^{-1}/4 X day) (Klassen, 2010)	Open label single-arm	44	Complete response 14/44 Partial response 12/44 Interrupted treatment 2/44 Died 16/44	Not reported	Sedation, infections, constipation, drowsiness
Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Thalidomide (OA 100 mg /4 X day) (Giaccone et al., 2005)	Open label single-arm	80 (29 Buccal)	Complete response 9/80 Partial response 5/80 Died 37/80	Complete response 8/29 Partial response 1/29	Sedation, constipation, neutropenia neuritis

Table 3. Systemic therapy using drugs of immunomodulatory effect.

Agent (dosage)[study]	Study design	n	Systemic results	Oral results	Main complications
Extracorporeal photopheresis (2- 5 cycles) (Parker et al., 1995)	Several open-label studies	59 (Buccal)	In different sites 39/59	Improvement 37/59	Low counts of red blood cells, platelets and neutrophils
Mycophenolate mofetil (OA adults 1 g /2 X day, or 20 mg kg^{-1} day^{-1}/ 2 X day under 50 kg) (Akpek, Lee, Anders, & Vogelsang, 2001)	Several open-label studies	Acute GVHD=19 Recurrent GVHD =29 Chronic GVHD=23	- Acute GVHD Partial response 3/19 Complete response 6/19 Treatment failed 10/19 Died 1/19 - Recurrent GVHD Partial response de 5/29 Complete response 9/29 Treatment failed 15/29 - Chronic GVHD Survival rate within 32 months 6/23 Need of additional treatment 13/23	- Acute GVHD: not reported - Chronic GVHD patients affected by treatment 18/23	- Acute GVHD: diseased not controlled for 3/19 patients. - - - Chronic GVHD gastric toxicity 4/23 patients
Mycophenolate mofetil (Children15-40 mg kg^{-1} /day) (Dall'Amico & Messina, 2002)	Open label single-arm	15	General response 9/15 Interrupted treatment 6/15	Complete response 5/15	Gastric toxicity, opportunistic infections

Extracorporeal photopheresis (Klassen, 2010) showed 63% improvement in oral manifestations of GVHD, although complications included low counts of red blood cells, platelets and neutrophils (Dall'Amico & Messina, 2002).

Topical and local therapy

Treatment of GVHD requires systemic treatment, but oral manifestations that do not subside with the systemic approach may benefit from topical and local therapy (Arora, 2008). Topical treatments may enhance healing of a particular body area, alleviating patients' systemic immunosuppression (Imanguli, Pavletic, Guadagnini, Brahim, & Atkinson, 2006). Several topical agents are currently used for the treatment of oral manifestations of GVHD, such as mouthwashes and topical immunosuppressants (Steroids, Cyclosporine, Azathioprine). Unquestionably, adequate oral hygiene is important to prevent oral infections, as well as the use of some agents that act on prevention and management of complications related to xerostomia, such as topical fluoride, saliva substitutes, and sialogogue pilocarpine (Elad, Or, Garfunkel, & Shapira, 2003a; Elad, Or, Resnick, & Shapira, 2003b).

The topical drugs reviewed were divided into two categories:

(a) Those of low absorption by the oral mucosa: Cyclosporine, Tacrolimus, Azathioprine and Budesonide. (Table 4)

(b) Those with action on tissue growth factors: local Phototherapy and Platelet gel. (Table 5).

Table 4. Topical treatment using drugs of low absorption by the oral mucosa.

Agent (dosage)[study]	Study design	n	Oral results	Main complications
Budesonide (3 mg 5mL^{-1} saline solution /2-3 X day /3months) (Elad, Or, Garfunkel, & Shapira, 2003a)	Open label single arm	12	Partial response 2/12 Complete response 2/12	No
Group B+ P+C: Budesonide (capsule 3 mg, dissolved in 10 mL water /3-4 X day) + Prednisone (2 mg Kg^{-1}/ day PO or IVA) + Cyclosporine (6 mg kg^{-1}/day PO or 3 mg Kg^{-1}/day IVA) Group B: Budesonide (capsule 3 mg dissolved in 10 mL water) /3-4 X day) (Sari et al., 2007)	Open label double-blind	B+P+C=12 B=11	- B+P+C: Complete response 3/12 Partial response 7/12 - B: Complete response 1/11 Partial response 3/11	Burning sensation, herpes viruses
Budesonide (3 mg 10 mL^{-1} dissolved in water) Group A: 10 min. / 3 X day; Group B: 5 min. / 3 X day ; Group C: 10 min. / 2 X day; Group D: 5 min. / 2 X day (Elad et al., 2012)	Open label randomized 4 arms	A=4; B=5; C=4; D=5	Objective response A: 2/4 ; B: 2/5 C: 3/4 ; D: 4/5 General response: 11/18 Interrupted treatment 3/18	Changes in taste, fungal infections, gastrointestinal disorders
Topical Cyclosporine (100 mg mL^{-1} in 0.5 mg dL^{-1} Zilactin / 4 X day) (Epstein & Truelove, 1996)	Open label single arm	18	Improvement according to patients 16/18 Improvement according to clinical evaluation 13/18 Interrupted treatment 1/18	Unpleasant taste
Cyclosporine mouth wash (100 mg mL^{-1}5 mL^{-1}/ > 1 min. (Epstein & Reece, 1994)	Open label single arm	11	Over 50% severity reduction 7/11 10% severity reduction 2/11 No response 2/11	Unpleasant taste
Topical Tacrolimus (ointment 0.1% / 2 X day) (Albert et al., 2007)	Open label single arm	6	Complete response 2/6 Partial response 4/6 Interrupted treatment for being satisfied with results 4/6	Burning sensations 1/6, discomfort after eating 1/6
Topical Tacrolimus (ointment 0.1% / 2-3 X day) (Greinix et al., 1998)	Open label single arm	18	General response 13/18 Died 5/18	Discomfort 1/18
Topical Tacrolimus (ointment 0.03-0.1% / 2-3 X day) (Elad, Or, Resnick, & Shapira, 2003b)	Open label single arm	10	Full recovery 1/10 Good response 2/10 Moderate response 4/10 No response 3/10 Died 3/10	Not reported
Tacrolimus solution (2.5 mL) + Topical Dexamethasone (2.5 mL) / 4 X day) (Mawardi, Stevenson, Gokani, Soiffer, & Treister, 2010)	Open label single arm	14	- Erythema Improvement 7/14 Stable 6/14 Worse 1/14 - Lichenoid reaction Improved 7/14 Unaffected 7/14	Not reported
Topical Azathioprine ointment or gel (5 mg cc^{-1}/ 3-4 X day) (Epstein & Reece, 1994)	Open label single arm	6	Complete response 4/6	Not reported
Topical Azathioprine ointment or gel (5 mg cc^{-1}/ 3-4 X day) (Epstein, Gorsky, Epstein, & Nantel, 2001)	Open label single arm	6	General improvement 4/6 Improvement ulcers 3/6 Improvement erythema 3/6 Less pain 4/6 Improvement vesicular-bullous lesions 2/6	Not reported

Table 5. Topical treatment using drugs with action on tissue growth factors.

Agent (dosage)[study]	Study design	n	Oral results	Main complications
Local phototherapy (2 consecutive days / every 2 weeks or once week until improvement takes place) (Perotti et al., 2010)	Open label single arm	25 (13 Buccal)	General improvement 15/25 Healing improvement 6/13 Improvement of Mouth opening 3/13 Died 10/25	Infections, renal failure, gastrointestinal bleeding
Local phototherapy (2 X month for 4 months + once month for 3 months) (Greinix et al., 2011)	Open label single arm	11 (4 Buccal)	Mucositis improvement 3/4 Interrupted treatment 2/11 Died 1/11	Hypotension 1/11
Local phototherapy (first month: 2 consecutive applications every week, total 8 applications + 2 consecutive applications every week 2 or 4 weeks) (Picardi et al., 2010)	Open label single arm	58 (27 Buccal)	General improvement 33/58 Lesions improvement 18/27	Not reported

Agent (dosage)[study]	Study design	n	Oral results	Main complications
Local phototherapy (3 applications first week for; twice week up to 12th week; 2 monthly applications up to 24th week) (Choi & Ngheim, 2001)	Open label single arm	29 (20 Buccal)	Mucosa improvement 14/20	Infections, bronchopneumonia, vascular access problems
Local phototherapy (3-5 X week) (Bisaccia et al., 2006)	Open label single arm	7	Complete skin response 3/6 Died 4/7	Hematological complications, infections
Local phototherapy (2 consecutive days with 1 week interval for 1 month + every 2 weeks for 2 months + once month, for total 6 months) (Child et al., 1999)	Open label single arm	41	Complete response 16/41 Partial response 11/41 Died 8/41	Not reported
Local phototherapy (2 applications repeated 3 times week + 2 applications / 2 weeks repeated 3 times + 2 applications/month) (Tsirigotis et al., 2012)	Open label single arm	102	Complete response 16/102 Partial response 38/102 Minimal response 28/102 No response 20/102 Died 22/102	Not reported
Local phototherapy (3 X week/alternate days) (Epstein, Nantel, & Sheoltch, 2000)	Open label single arm	14 (7 Buccal)	Complete skin response 3/14 Partial skin response 4/14 Skin stabilization 7/14 Complete buccal response 1/7 Buccal improvement 2/7 Lesions stabilized 3/7 Buccal lesions worsened 1/7 Interrupted treatment 3/14 Died 3/14	No
Local phototherapy (2 applications/week repeated twice; 2 applications every 2 weeks repeated 3 X; 2 applications month) (Calore et al., 2008)	Open label single arm	Acute GVHD= 50 (8 Buccal) Chronic GVHD= 23 (5 Buccal)	- Acute GVHD General response 34/50 Oral mucosa response 7/8 - Chronic GVHD General response 16/23 Oral mucosa response 4/5	Infections
Local phototherapy (2-4 X week) (Couriel et al., 2006)	Open label single arm	71 (9 Buccal)	Complete response 14/71 Partial response 29/71 Oral improvement 7/9 Died 42/71	Not reported
Local phototherapy (Not reported) (Fante, Scudeller, Viarengo, Bernasconi, & Perotti, 2012)	Open label single arm	32 (25 Buccal)	Determinant of the cure 7/32 General improvement 18/32 Inefficient 7/32 Complete response 16/25 Partial response 7/25 Condition stabilized 2/25	Not reported
Local phototherapy (2 consecutive days with 2 weeks interval for 3 months + once every 4 weeks up to recovery) (Bisaccia et al., 2003)	Open label single arm	15 (11 Buccal)	Complete response 11/11 Died 1/15	Infections
Local phototherapy (3 X week/alternate days) (Rubegni et al., 2005)	Open label single arm	6	Skin improvement 6/6 Smoother skin 4/6 Oral lesions stabilized 2/6	Not reported
Local phototherapy (0.02 mJ cm^{-2}/2-3 X week) (Enk et al., 1998)	Open label single arm	5	Scleroderma: improvement dryness and itching 2/5 Lichenoid reaction: complete cure Buccal lesions: subjective improvement Interrupted treatment 1/5	No
Local phototherapy Group Phototherapy (P): (0.5 J cm^{-1}/ 3 X week for 4 weeks) Group Dexamethasone (D): (mouth wash 0.1 mg mL^{-1}/ 4 X day) (Wolff et al., 2004)	Open label double - blind	P=7 D=16	- P Complete response 4/7 Partial response 2/7 - D Complete response 9/16 Partial response 2/16	Nausea due to Psolaren-UVA, candidosis in group D
Platelet Gel (spray / 2 X week) (Duzovali & Chan, 2007)	Open label single arm	6	Complete ulcer re-epithelialization 5/6 No more pain 6/6 Complete cure 2/6 Died 1/6	Burning sensation and itching on first application

Discussion

A growing body of research has focused on finding ways to improve both the quality of life and the survival rate of patients with GVHD (Lee, Dörken, & Schmitt, 2004). The difficulty in choosing the appropriate treatment for GVHD lies in the diversity of organs involved, the acute or chronic nature of the disease, and the hematologic and immunologic disorders associated with the syndrome (Ratanatharathorn, Ayash, Lazarus, & Uberti, 2001).

Systemic treatment is needed for more severe manifestations of the disease, especially when multiple organs are involved (Socie, Ritz, & Martin, 2012). Among the therapeutic currently available, systemic therapies are the most used due to the

general nature of the disease, whether chronic or acute. However, long-term systemic treatment increases the risk of infections, recurrence of cancer, and risk of squamous cell carcinoma of oral mucosa (Wang et al., 2009).

Corticosteroids are still the first-line drugs used for GVHD, such as Methylprednisolone associated or not with Cyclosporine (Bisaccia et al., 2003). They are inflammatory mediators and useful as prophylactic treatment (Akpek et al., 2001), they act by preventing healthy tissues from responding to inflammatory processes, and inhibiting the release of inflammatory chemical mediators, making patients less susceptible to manifestations of GVHD.

Immunosuppressants are also front-line drugs to treat GVHD, as they inhibit T and B lymphocytes proliferation, thereby reduce the response of the body against the grafted tissue and improve the chances of successful transplantation (Wolff et al., 2004). Cyclosporine, Pentostatin, Rituximab and Sirolimus are among the most commonly used immunosuppressants.

Tacrolimus, also an immunosuppressant, has few side effects and, for this reason, is especially recommended for patients with liver failure as salvage therapy (Carnevale-Schianca et al., 2000).

Immunomodulatory drugs, such as Hydroxychloroquine, Mycophenolate mofetil, Thalidomide, and Methotrexate, may be associated to systemic therapy in order to improve the treatment. They are alternatives for patients who do not respond well to treatment (Moreira, De Medeiris, Bonfim, Pasquini, & De Medeiros, 1998).

Extracorporeal phototherapy is another immunomodulatory effective therapy on skin and oral injuries (Enk et al., 1998). It can prevent long-term complications when associated with steroids, and reduces the response-time to treatment (Bisaccia et al., 2003).

GVHD can affect specific sites with great intensity, cases that require supplementary topical drugs in order to reduce the risks involved in systemic therapy (Arora, 2008). Due to their low bioavailability, one of the main advantages of topical drugs, such as Budesonide and Cyclosporine, is their reduced systemic side effects when absorbed through mucous membranes (Elad, Or, Garfunkel, & Shapira, 2003a).

Topical Cyclosporine is effective to treat lichen planus and ulcerative lesions, common GVHD conditions (Epstein & Truelove, 1996), as well as topical Tacrolimus, widely used in dermatology for the treatment of such injuries (Eckardt, Starkea, Stadler, Reuter, & Hertenstein, 2004).

Mouth ulcers as an oral manifestation of GVHD impact patients' quality of life. Treatment can be done with topical Azathioprine, which reduces the pain caused by ulcerations (Epstein, Gorsky, Epstein, & Nantel, 2001). Platelet gel is also used to treat mouth ulcers, given that it releases growth factors that stimulate re-epithelialization, which, in turn, lead to tissue regeneration (Fante, Scudeller, Viarengo, Bernasconi, & Perotti, 2012).

However, the articles reviewed lack enough evidence about the effectiveness of topical therapies. All patients were receiving concomitant systemic treatment of different types, and often the dosages of the topical drug were not specified, which hinder definite conclusions.

Further research on oral manifestations of GVHD is needed, as the articles reviewed showed that topical treatment only showed positive results on oral lesions, whereas few studies analyzed the impact of systemic therapy in the mouth.

A deeper knowledge of the disease's pathophysiology is also needed, since it is the functional changes caused by GVHD that determine where the drugs can work. Therefore, studies on the mechanisms of GVHD in the oral cavity, as well as well-designed clinical trials are urgently needed, as they might provide means for better management of the disease and for improving patients' quality of life.

Conclusion

The articles reviewed showed that systemic therapy, despite its high risks of side effects, is still the most used for the treatment of chronic GVHD. Methylprednisolone and corticosteroids were the first choice for systemic treatment of the disease. As for topical and local therapy, Tacrolimus and topical Cyclosporine showed positive results on oral manifestations.

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