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Topical treatment of oral chronic graft-versus-host disease in hematopoietic stem cell transplant recipients: A Systematic Review

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LIST OF SYMBOLS AND ACRONYMS

Ab	Antibody
Ag	Antigen
aGVHD	Acute graft-versus-host disease
APC	Antigen presenting cell
ASBMT	American Society for Blood and Marrow Transplantation
BM	Bone marrow
BMSC	Bone marrow stem cell
CASP	Critical Appraisal Skills Program
cGVHD	Chronic graft-versus-host disease
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
COVID-19	Corona virus disease 19
CSA	Cyclosporine
CT	Computerized tomography
DNA	Desoxyribonucleic acid
DMQ	Dry Mouth Questionnaire
EBMT	European Society for Bone and Marrow Transplantation
G-CSF	Granulocyte colony stimulating factor
GVHD	Graft versus host disease
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
IL	Interleukin
MA	Myeloablative
mAb	Monoclonal Antibody
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MMUD	Mismatched unrelated donor
mOMRS	Modified Oral Mucosal Rating Scale
MRD	Matched related donor
MTX	Methotrexate
MUD	Matched unrelated donor
NIH	National Institute of Health
NMA	Nonmyeloablative
OMAS	Oral Mucositis Assessment Scale
PAM	Pre-transplantation Assessment of Mortality
PB	Peripheral blood
PBSC	Peripheral blood stem cell
PCR	Polymerase chain reaction

PICO	Population, Intervention, Comparison, and Outcome
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
RIC	Reduced intensity conditioning
SARS CoV-2	Severe acute respiratory syndrome coronavirus
SFR	Salivary Flow Rate
TBI	Total body irradiation
Tc	T-cytotoxic
Th	T-helper
UCB	Umbilical cord blood
UCBSC	Umbilical cord blood stem cell
UV	Ultraviolet
VAS	Visual Analogue Scale
WHO	World Health Organization

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ABSTRACT

Background

Graft-versus-host disease is a common complication of hematopoietic stem cell transplantation and one of its main manifestations sites is the oral cavity. This systematic review compares different Randomized Controlled Trials with the objective to investigate the best option available for the topical treatment of oral graft-versus-host disease.

Materials and methods

A systematic search was carried out using the four databases: PubMed, Medline complete, Cochrane, and Scopus, following the PRISMA guidelines. Studies included were RCTs published between January 2011 and March 2022 in English, Spanish, or German language that included patients with oral graft-versus-host disease receiving topical treatment. An overall of five RCTs were included (two Randomized Double-Blind Clinical Trial; an Open, Randomized, Multicenter Trial; an Open-Label Phase II Randomized Trial; and a Randomized Clinical Trial). Risk of bias was evaluated following the CASP checklist for RCTs.

Results

The trials involved a total of 157 patients: 44 patients received topical dexamethasone, 18 patients received topical budesonide, 14 patients received malic acid, 14 patients a placebo, 14 patients received topical clobetasol, 14 patients received topical tacrolimus, 13 patients received triamcinolone in orabase, and 13 patients received curcumin in orabase. Budesonide caused the highest overall treatment response. Malic acid, clobetasol, and dexamethasone increased resting salivary flow rates. Curcumin in orabase shows results similar to standard corticosteroid treatment. The mean duration of treatment was 4.4 weeks, ranging between 2 and 8 weeks. Adverse effects were observed in budesonide, dexamethasone, clobetasol, and tacrolimus population, none of them were severe.

Discussion

Given the small number of RCTs performed and the heterogeneity of the different study designs, it is difficult to draw direct comparisons and conclusions. Malic acid appears to be effective for the treatment of graft-versus-host disease-induced xerostomia. Budesonide had the highest overall response rates for the topical treatment of oral graft-versus-host but was also associated with the highest number of adverse effects. Larger studies are currently being conducted to further investigate its effectiveness. An alternative to corticosteroid therapeutics could be curcumin in orabase, which long has been in use in Southeast Asia, however further studies are needed to validate these results.

Conclusion

According to this systematic review, budesonide is the best studied and most promising treatment option in terms of overall treatment response. The average duration of treatment for all therapeutics was 4.4 weeks. Most reported side effects were in the patient groups receiving budesonide.

KEYWORDS

Hematopoietic stem cell transplant, oral graft-versus-host disease, topical treatment, topical corticosteroids

1. INTRODUCTION

1.1. Hematopoietic stem cell transplants

Stem cells are unspecialized human cells with the capacity to differentiate into any cell of the organism and the ability of self-renewal. Hematopoietic stem cells (HSCs) are multipotent cells that have a narrower spectrum of differentiation meaning they can specialize in discrete cells of specific cell lineages. HSCs generate all functional hematopoietic lineages in blood like erythrocytes, leukocytes, and platelets (1).

Hematopoietic stem cell transplants (HSCTs) aim to counteract problems related to the inappropriate functioning of the hematopoietic system, like hematologic malignancies and genetic diseases (1,2). The rationale of HSCTs is to achieve a broad lymphoablation that allows an initial breakdown of the immunological memory repertoire. As a result, the hematopoietic and thus the immune system is regenerated, which enables an immunological renewal. This process includes the diversification of the T cell receptor repertoire and a renewal of the regulatory T and B cell compartments (3).

The first procedure was carried out in 1957 by E. Donnell Thomas and even though success rates were low in the beginning, with time the procedure techniques and pharmacological treatments improved and therefore, around 60.000 transplantations were performed worldwide in 2016 according to the Center for International Blood and Marrow Transplant Research (2,4). An overall of 1.298.897 HSCT procedures have been recorded between 1957 and 2016 (5).

There are different types of HSCTs whose classification depends on the source of the graft or the relationship of the donor and recipient. The stem cells are either obtained from peripheral blood (PB), bone marrow (BM), or umbilical cord blood (UCB) (1,2). Regarding the relationship, the transplant can either be autologous, allogeneic, or syngeneic (1). In autologous transplants, the donor and recipient are the same person. In allogeneic transplants the recipient receives the stem cells from a sibling or a third-party donor (2). In syngeneic transplants, the cells from an identical twin are used (1). Most autologous transplants use peripheral blood stem cells (PBSCs) due to the ease of collection and its association to a more rapid hematopoietic recovery (6).

1.1.1. Indications

In general, HSCTs are indicated in many malignant and nonmalignant hematologic disorders, other neoplastic disorders, and severe immunologic deficiencies (3,7).

Whether an allogeneic or autologous HSCT is indicated, depends on the modality that has shown better outcomes in clinical studies. Leading indications for autologous transplants are multiple myeloma and lymphoma (2). Allogeneic HSCTs are beneficial in diseases in which graft-versus-tumor effect has been demonstrated, meaning that the graft's T cells attack the remnant malignant cells of the recipient. Leading indications for allogeneic HSCTs are: Acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndromes, and myeloproliferative neoplasms. HSCT has also shown to be effective in the treatment of select solid tumors like germ cell tumors, neuroblastoma, Ewing sarcoma, and medulloblastoma (2,7).

Furthermore, HSCTs can be indicated in nonmalignant conditions, such as: Severe aplastic anemia, inherited bone marrow failure syndromes, sickle cell disease, transfusion-dependent thalassemia, inherited immune deficiency syndromes and certain metabolic disorders (2).

In the past years, research also focused on investigating the effectiveness of HSCTs following high-dose chemotherapy for the treatment of severe refractory autoimmune diseases (2,3). In Europe between 1994 and 2019, 3.320 HSCT procedures treating autoimmune diseases were registered to the European Society for Bone and Marrow Transplantation (EBMT) registry. 3.103 patients received autologous transplants, whereas 217 had undergone allogeneic transplants. Main indications for autologous HSCTs were multiple sclerosis, systemic sclerosis, Crohn's disease, inflammatory arthritis, and systemic lupus erythematosus (3).

1.1.2. Hematopoietic stem cell sources

Stem cells are commonly obtained from the BM, PB, or UCB. For autologous HSCTs, cells obtained from PB are the preferred choice as it is associated with a more rapid hematopoietic renewal. Valid options for allogeneic HSCTs are bone marrow stem cells

(BMSCs), PBSCs, and umbilical cord blood stem cells (UCBSCs), depending on the given circumstances (2,7).

Bone marrow

BM as a source for the acquisition of HSCs was considered the gold standard for more than a decade after the first transplant was performed in the 1950s (2,8).

However, the number of cells obtained during this procedure has not been adequate in many cases and therefore is no longer considered the preferred method today (8). The load of T cells is less compared to other graft sources which is why the probability of developing chronic graft-versus-host disease (cGVHD) is also decreased (9). However, the procedure of obtaining the cells is more invasive for the donor and bears higher risks itself, most of which are related to the anesthesia. Also, infection, blood loss and pain are some of them and in rare cases, even potential morbidity risk (10).

Peripheral blood

Nowadays, mobilized PBSCs are more commonly used than the cells obtained from BM (2,6). Under normal conditions, the percentage of HSCs in PB is low, however, by administering recombinant granulocyte colony stimulating factor (G-CSFs), HSCs are mobilized from the BM and increase the number of circulating CD34+ progenitor cells in the blood. Despite the rapid recovery of hematopoiesis, one major advantage of this procedure is that it involves a much less invasive cell-harvesting approach compared to the acquisition of cells from BM (8). However, the load of T cells is higher compared with BM explaining the increased rates of cGVHD (2,7,8). Due to its association with cGVHD, it is not a preferred option for pediatric patients and patients with early-stage diseases (7).

Umbilical cord blood

Over the last decades, UCB has become an alternative source for HSCs. A big advantage is that it allows for a higher human leukocyte antigen (HLA) disparity than the other sources, which also increases the likelihood of finding a suitable donor (11). In addition, it is quick to obtain and access and not harmful to the donor. Furthermore, it is linked to a comparatively low risk of developing GVHD. However, disadvantages

include slow engraftment and immune renewal and, consequently, the increased risk of developing infections (9).

1.1.3. Donor selection

Choosing an adequate donor is crucial for the outcome of a HSCT and several factors must be taken into consideration. First, genetic matching plays an important role, more precisely, HLA compatibility (2,12). HLA is a set of genes on chromosome 6 encoding for the major histocompatibility complex (MHC). Those antigens (Ags) play a decisive role in the immune function and are involved in graft rejection, infection control and autoimmunity which might lead to a failure of engraftment. The most important HLA genes linked to HSCTs are HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1, and HLA-DPB1 (12). Also, to reduce the risk of GVHD and potential mortality, choosing an HLA potential compatible donor is crucial (13). Stem cells can derive from related, but also unrelated donors:

Matched related donors

HLA-identical sibling donors remain to be the preferred donor type over others (13,14)However, only 25-30% of the patients have this option (13). Due to the decreased availability, research has also focused on using unrelated donors, mismatched family member donors and unrelated UCB, as source for HSCs (11).

Matched unrelated donors

In that case, donor and recipient are not related, making it less probable to find a suitable donor due to the diversity of HLA alleles and haplotypes (13). A matched unrelated donor (MUD) is defined as a 10/10 or 8/8 identical donor based on HLA typing for Class I (HLA-A, -B, -C) and Class II (HLA-DRB1, -DQB1) (7). According to American standards, an 8/8 match for the loci HLA-A, HLA-B, HLA-C, and HLA-DRB1 and according to the European standards 10/10 for the loci HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1 are required (12). Even though matched related donors (MRDs) remain the preferred donor source, survival rates after the HSCT are comparable nowadays among patients receiving the cells from MUDs (14).

As not all patients might have an HLA identical sibling or MUD available, other donor sources like mismatched unrelated donors (MMUDs), haploidentical donors or UCB must be taken into consideration:

Mismatched unrelated donor

MMUD is an unrelated adult donor with a mismatch of at least one Ag or allele at HLA-A, -B, -C, or -DR. However, there seems to be a difference in outcomes, depending on what allele is affected. It is distinguished between “permissive” and “non-permissive” HLA mismatch (7).

Haploidentical donors

Haploidentical donors are family members where only one HLA haplotype is genetically identical with the recipient, meaning that parents, siblings, and children may be suitable donors. Some advantages are the availability, easy access, choice of best donor and rapid obtainment of the graft. One of its major disadvantages used to be the association with host-versus-graft and graft-versus-host responses. However, thanks to advances in conditioning regimen, results are now similar to recipients receiving HSCs from MUD (7).

Umbilical cord blood

Unrelated UCBSCs are used especially when no MRDs or MUDs are available. Selection of cord blood units depends on HLA matching and the dosage of cells. The maximum HLA disparity consists of 2/6 defined by HLA-A, -B Ag, and HLA-DRB1 allele typing. A minimum dose of 2.5 - 3×107 nucleated cells/kg body weight of recipient at collection or 2×107 nucleated cells/kg at infusion is recommended, however, the type of disease also influences the required dose (7).

Despite the graft type and HLA match, other factors are also important when it comes to choosing a suitable donor. Advanced age of the donor for example can increase the risk of aGVHD and cGVHD and therefore negatively influence the overall survival rate (15,16). Also, infections with the cytomegalovirus (CMV) play an important role. Seropositive recipients should receive cells from a CMV seropositive donor, whereas seronegative patients should be receiving cells from a seronegative donor.

However, in many studies, adverse effects of seropositive donors in seronegative or seropositive recipients could not be detected (15,16).

Regarding the AB0 compatibility, many outcomes have been evaluated and results varied also depending on the setting. In some studies differences in outcome were registered depending on the type of graft source. PBSC grafts did not seem to negatively influence the outcome of the transplants, whereas when BM was used as a source, it negatively affected the survival (16). Especially in T-cell replete haploidentical donor transplants using post-transplantation cyclophosphamide, an AB0 compatible graft should be chosen over a minor and/or a major AB0 mismatched graft. Also, a PB graft is the preferred source option in major donor-recipient-AB0 incompatibility (16).

Some studies suggest that sex match also plays an important role when choosing an adequate donor. An increased risk of cGVHD and an increased risk of transplant-related mortality in male patients receiving transplants from female donors has been documented (15,17).

In case of female donors, it is recommended to use non-parous female donors as there is an increased risk of developing HLA-specific antibodies caused by the exposure to fetal Ags in utero in parous females. Research suggests that recipients receiving a HSCT from a parous donor have a higher risk of developing cGVHD. However, in some studies there was no association of the development of acute graft-versus-host disease (aGVHD) and the donor sex (15).

The corona virus disease 19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) represents one of the greatest challenges of the 21st century and may also play an important role in dealing with HSCT recipients. Especially because most patients who qualify for an HSCT also fall into the coronavirus risk group (18). The EBMT published recommendations in 2020 on how to deal with these patients. Polymerase chain reaction (PCR) testing for SARS-CoV-2 should be taken before the transplant. In case of positive PCR results, HSCTs should be delayed until the recipient tested negative. However, this decision is based on individual needs of the patients, as the underlying disease might be at risk for progression. Also, chest imaging by computerized tomography (CT) scan should be carried out in all patients tested positive SARS-CoV-2 (19). Also, the donors must be tested for the presence of SARS-CoV-

2, and in case of a positive test result, donors must be excluded from donation (19). Despite those considerations, every donor must be submitted to a thorough screening to make sure the donor is in a healthy physical condition, does not have any infectious diseases and qualifies psychologically.

1.1.4. Patient eligibility/ assessment criteria

The final decision if a patient benefits from a HSCT is a multifactorial decision including factors like the patient's overall health and performance status, the presence of comorbidities, disease risk/ status, as well as the graft and donor source (14). There are no uniform guidelines which is why the eligibility of each patient must be assessed individually, preferably from an interdisciplinary team (20). However, the American Society for Blood and Marrow Transplantation (ASBMT) and the EBMT introduced tools to provide guidance on assessment and eligibility of patients (14,21).

Advanced age itself should not be a contraindication to determine the patient's eligibility, however it does play an important factor when choosing a patient, since the likelihood of suffering from comorbidities increases with advanced age (21). There are a variety of comorbidity indices aiding in the assessment of eligibility. Some commonly used ones are the Kaplan-Feinstein scale, Pre-transplantation Assessment of Mortality (PAM) score, EBMT risk score, and the Hematopoietic cell transplant-specific comorbidity index (14,20).

Furthermore, patients undergo a thorough physical assessment, performance status and geriatric assessments, pulmonary and cardiac evaluation, hepatic and renal function evaluation, nutritional evaluation, and a dental evaluation (20). Another important factor is the psychological assessment prior to the HSCT, which can be specific or non-specific for the HCST and addresses topics like distress, anxiety and depression, substance abuse, financial and socioeconomic status, and caregiver considerations (20).

1.1.5. Conditioning regimen

Before the transplantation, patients suffering from malignant disease are submitted to a conditioning regimen to reduce the tumor burden in neoplastic diseases and

suppress the recipient's immune system to allow engraftment of stem cells and avoid rejection (22,23). Conditioning regimens include irradiation, chemotherapy, serotherapy, monoclonal antibodies (mAbs), and targeted therapy depending on the malignancies and types of donors. Its main aims are to obtain myelodepletion of the host stem cells and lymphodepletion of the host lymphoid system. Traditionally, conditioning regimens have been myeloablative (MA) in nature. The term MA refers to exposure to total body irradiation (TBI) and/ or alkylating agents at doses which do not allow autologous hematologic recovery (22). The most applied ones were a combination of high-intensity TBI of 12Gy to 16Gy and a chemotherapeutic agent, usually cyclophosphamide. Other agents like cytarabine, etoposide, melphalan, and busulfan have also been used. There is still no consensus on what the most effective option is (24).

However, those protocols have been associated with higher rates of organ- and transplant-related toxicity, leaving a narrow therapeutic window and making the transplant less suitable for older patients (22). Research in the last two decades focused on non-myeloablative (NMA), reduced intensity conditioning, and reduced toxicity conditioning regimens to counteract those undesired side effects. In the 1970s and 1980s, it was observed that immunologic reactions of donor cells against the malignant host cells (e.g., graft-versus-tumor effect) can potentially increase the effectiveness of a HSCT. Therefore, reduced intensity conditioning (RIC) and NMA conditioning regimens have been developed. Due to their positive association with the graft-versus-malignancy effect, they rapidly gained popularity and by 2001 already 30% of the transplants were performed with reduced intensity regimens (22).

Regarding RIC, the therapy can consist of chemotherapeutic agents only or a combination of reduced intensity 4Gy TBI and chemotherapeutic agents. However, there are no uniform guidelines and no consensus on what the most effective method is (24).

In case of the NMA regimens, many regimens include a low-dose of 2-Gy TBI. However, due to low irradiation, the leading cause of treatment failure was relapse and consequently mortality, as proven in studies (24).

In more recent research, radioimmunotherapy-based regimens have been developed in autologous and allogeneic HCST settings, including radiolabeled mAbs like Anti-CD20 radioimmunoconjugates and Anti-CD45 radioimmunoconjugates. In those cases, higher doses of radiation are directed to the tumor site, whilst the rest of the body is spared from radiation. Other regimens contain antibodies (Abs) targeting T lymphocytes which are combined with high-dose or RIC regimens.

In general, there are no standardized conditioning regimen and factors like, characteristics of the host like age, comorbidities, and refractory disease, but also the type of HSCT must be taken into consideration, when choosing an adequate conditioning regimen. However, with the introduction of RIC regimens, allogeneic HSCT have been made accessible to older patients as well as patients with poorer general health conditions (24).

1.1.6. Complications

Regarding the time of occurrence, complications are classified into three groups: complications of the pre-engraftment period, early post-engraftment, and late post-engraftment period (2).

In the pre-engraftment period, complications occur between the start of the conditioning regimen until the neutrophil recovery. Consequently, pancytopenia, gastrointestinal toxicities, and organ dysfunctions may occur (25). The type of graft, transplantation procedure, underlying disease, conditioning regimen, and the presence of comorbidities determine its prevalence, gravity, and course (2).

The early post-engraftment period complications are observed in the period from neutrophil recovery to 100 days post transplantation. Despite the neutropenia recovery, cellular and humoral immunity are still compromised and therefore the risk of suffering infections remains. Especially opportunistic infections like *Pneumocystis jirovecii* and CMV infections, but also respiratory viruses like influenza, respiratory syncytial virus and adenovirus are common. Furthermore, this period is associated with an increased risk of developing the aGVHD (2,25,26).

In the late post-engraftment period, complications occur beyond day 100 of the transplantation (2). During that phase cellular and humoral immunity reconstitution

continues (26). It is associated with a risk of cGVHD and thus the development of opportunistic infections (2).

1.2. Graft-versus-host disease

The major lethal complication of HSCT is the GVHD, an immunological disorder in which the donor's lymphocytes attack the healthy recipient's tissues. The disease has first been observed and described by Barnes and Loutit in 1955 during HSCT studies in animals (27). Most likely it is associated with allogeneic HSCT, whereas its occurrence after blood product transfusion, solid organ transplants, or autologous HSCT is rare (28). The incidence rate lies between 40-60% of which 15% are lethal (28). Given the current trend, the number of transplants from unrelated donors is expected to double within the next 5 years and will substantially increase the number of patients with GVHD. The threat posed by GVHD to patient survival is also gradually increasing (4). The major risk factor determining GVHD development is the HLA disparity which is why thorough high-resolution desoxyribonucleic acid (DNA)-matching should be carried out before the transplantation. Other common risk factors associated to GVHD are donor/ recipient sex mismatch, especially between female donors and male recipients, advanced age of the recipient, choice of progenitor cell source, pre-transplantation manipulations and graft composition, and the intensity of the conditioning regimen (26).

1.2.1. Classification

In general, GVHD may affect many organs of the body. According to distinct clinical features and underlying pathophysiologic mechanisms, it can be distinguished between aGVHD or cGVHD (4,25,26).

Acute Graft-versus-host disease

Due to chemotherapy, radiotherapy and/ or immunosuppressive medications during the conditioning phase, exogenous and endogenous molecular activators of the immune response are released causing an increased expression of MHC-Ags and adhesion molecules. Those processes lead to an increase in the recognition of host allo-Ags by donor T-cells which interact with host antigen presenting cells (APCs) providing

costimulatory signals leading to donor T-cell activation and expansion into T-helper-1 (Tantigh1), T-cytotoxic (Tc), and Th17/Tc17 subtypes. Through molecular attractants and receptor interactions, cytotoxic effector T-cells reach the target organs. The aGVHD response is amplified by a feedback loop resulting from the activation of mononuclear phagocytes via lipopolysaccharides released during the initial tissue damage (25,26)

aGVHD primarily manifests in the skin, liver, gastrointestinal tract, but has also been associated with the oral cavity (29). It is classified into four types according to the extent of involvement of the affected tissue: I (mild), II (moderate), III (severe), and IV (very severe) (4,26).

Chronic Graft-versus-host disease

The pathophysiology of cGVHD is established by three phases. In the first phase, innate immune cells and nonhematopoietic cells like endothelial cells or fibroblasts are activated due to processes like cytotoxic injury, infections and aGVHD. Consequently, inflammatory mediators, such as interleukin 33 (IL-33) and pathogen-associated molecular patterns like lipopolysaccharide are released. In the second phase, hyperresponsiveness of the adaptive immune system and the subsequent reduction of immune cell regulators occurs. An immune response to host foreign MHC proteins occurs leading to the upregulation of Th1, Th2, and Th17 cells with a reduction in regulatory immune cells such as regulatory T-cells. The third phase is characterized by abnormal tissue repair triggered by activated macrophages which cause the activation of fibroblasts. Due to their activation, the fibroblasts produce extracellular matrix collagen and biglycan stimulating tissue stiffness. This process is amplified by Th17 cells that were upregulated during the second phase (25).

Due to the severe immunosuppression in cGVHD, recurrent infections play a major role and are directly related to the morbidity and mortality of the patients with cGVHD (25). In general, cGVHD is subdivided into two types: limited cGVHD and extensive cGVHD (4).

1.2.2. Manifestations

In general, GVHD is a multisystemic disorder affecting several organs of which skin manifestations are the most common ones (24,25). However, in this review, it will be focused on the oral manifestations. In the aGVHD, oral manifestations are observed but the oral cavity normally is not a classic target organ. In cGVHD however, the mouth is one of the major affected sites, with more than 70% of the patients developing manifestations (29).

Common general oral manifestations include erythema, erosions, ulcers, lichenoid lesions, xerostomia, and pain (28). In some cases, mucoceles and mucosal atrophy have also been observed (25). In the aGVHD classic features are erythema, ulcerations, but also lichen planus-like hyperkeratotic lesions. Added to that, lip involvement with crusting can also be found (29). cGVHD is mainly associated with lichen planus-like features, hyperkeratotic plaques and restriction of mouth opening due to sclerosis. Depending on the site of affectation, it is distinguished between oral mucosal disease, salivary gland disease and sclerotic disease (29–31).

In the oral mucosa cGVHD, lichenoid inflammation involving the tongue and buccal mucosa has different degrees depending on their clinical presentation, tissue involvement and symptoms. Changes might include white papules, plaques, hyperkeratotic reticulations, erythema, and pseudomembranous ulcerations. Those presentations are associated with an increased sensitivity to spicy, acidic, rough, minty, and strongly flavored food (29,30,32).

In cGVHD of the salivary glands, a quantitative and qualitative alteration of the saliva occurs, leading to xerostomia and functional problems such as speaking and mastication difficulties and the increased prevalence of oral candidiasis. Furthermore, patients might develop rampant caries within the first 2-year post-transplantation (29,33).

In the sclerotic cGVHD, scleroderma-like manifestations like fibrosis and limited mouth opening and subsequent functional impairment can be observed. However, sclerotic involvement is less frequent (29).

1.2.3. Assessment of Graft-versus-host disease

Diagnosing cGVHD can be achieved by reviewing the patient's history, clinical findings, and context of onset (29). In 2005 a staging score was introduced by the National Institute of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in cGVHD which was updated in 2014. The introduced staging score includes a general performance score ranging from 0 to 3 and is based on subjective clinical assessment. Added to that, there are scores from 0-3 regarding the different organs that might be affected: Skin, mouth, eyes, gastrointestinal (GI) tract, liver, lungs, joints, and genital tract. Regarding the mouth, the grading score refers to the presence of lichen planus-like features, as described in table 1 (34).

Table 1: Modified from the oral staging score introduced by the NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (34).

Stage	Symptoms
0	No symptoms
1	Mild symptoms with disease signs but not limiting oral intake significantly
2	Moderate symptoms with disease signs with partial limitation of oral intake
3	Severe symptoms with disease signs on examination with major limitation of oral intake

Also in 2005, the "NIH Oral cGVHD Clinical Scoring Instrument" was developed which aims to be more objective and detailed. As we can see in table 2, it is a 0–15-point tool that stages the severity and extent of erythema, lichenoid hyperkeratotic changes, ulcerations, and number of mucoceles (28,29).

Table 2: Modified from NIH Oral cGVHD Clinical Scoring Instrument.

Mucosal change:	**No evidence of cGVHD**		**Mild**		**Moderate**		**Severe**	
Erythema	None	0	Mild erythema or moderate erythema (<25%)	1	Moderate erythema	2	Severe erythema (>25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>25%)	3
Ulcers	None	0	None	0	Ulcers involving (<20%)	3	Severe ulcerations (>20%)	6
Column Total			Column Total		Column Total		Column Total	
Oral surfaces scored: Vermillion lips, labial and buccal mucosa, tongue (dorsal, lateral, ventral), and soft palate;							Total score for all mucosal changes:	

1.2.4. Prevention

There are no general guidelines on prophylactic measures taken to prevent the occurrence of GVHD. In case of aGVHD, the preventive measures aim to suppress the donor cells. This is achieved by either methotrexate (MTX) and cyclosporine (CSA), MTX and tacrolimus, mycophenolate mofetil (MMF) and calcineurin inhibitor (CNI). In other studies, T-cell depletion has also shown promising results (28). In that case, when using bone marrow or mobilized peripheral blood as a source of hematopoietic progenitors, the aim is to reduce the concentration of T cells by at least 2-log. This has been linked to a significant decrease of GVHD in an allo-HSCT with an HLA-identical family donor (27).

Regarding the prevention of cGVHD, most preventive measures lack efficacy. The most effective ones tested so far, however, are anti-thymocyte globulin and rituximab (28).

1.2.5. Treatment

The first-line therapy for GVHD are systemic corticosteroids. However, due to their associated secondary effects like osteoporosis and avascular necrosis, other agents have also been indicated like: MMF, sirolimus, CNIs, mAbs and extracorporeal photopheresis. Regarding the management of oral GVHD, topical treatment can be either combined with systemic treatment or might be efficient as efficient as sole therapy (29).

There is no optimum treatment option available for the management of oGVHD, but therapeutics aim to reduce symptoms, maintain function, and improve quality of life (29,35,36).

Generally, there are pharmacological and non-pharmacological treatment options. Intensive topical corticosteroid therapy serves as first-line therapy (29,37). Common solutions used are dexamethasone, budesonide, prednisolone, and triamcinolone. Furthermore, there are high-potency corticosteroid gels which have shown effectiveness, such as fluocinonide gel, clobetasol gel, betamethasone dipropionate gel, and triamcinolone ointment. Non-steroidal alternative like tacrolimus or CSA are also valid options and can either be used as solution or ointment (29,38,39). Another option which is under current investigation is topical platelet-rich gel (39–41).

Non-pharmacological treatment options comprise different types of phototherapies, such as psoralen ultraviolet-A (UV-A) using intraoral psoralen sensitizers, UV-B therapy, low-laser therapy, carbon dioxide laser therapy, and photobiomodulation therapy. However, available data is limited, and further studies are required (29,42).

Furthermore, to ensure optimum oral health aiding the course of disease, regular dental evaluations are indicated due to the associated risk of caries and secondary malignancies (29,35).

2. JUSTIFICATION, HYPOTHESIS, OBJECTIVES

2.1. Justification

Thanks to advances in modern medicine in the past decades, outcomes of HSCTs have improved tremendously making it a valid treatment option for patients suffering from malignant or non-malignant hematopoietic diseases (2,3,7). Furthermore, in the past years it has also shown promising results in the treatment of patients with severe refractory autoimmune diseases. Due to the increased prevalence of those diseases and the improved medical therapeutic methods, the number of HSCT has risen, making it also more likely for dental practitioners to encounter those patients in their dental clinic. Despite recent advances in medicine, graft-versus-host disease remains to be a common comorbidity associated with HSCT recipients due to the immense immunosuppression. One of the major manifestation sites of GVHD is the oral cavity, highlighting the importance of the dentist not only in the early diagnosis of the disease but also in its topical treatment (28,29).

This systematic review aims to compare the topical treatment options available for the treatment of oral chronic GVHD to investigate the most effective option.

2.2. Hypothesis

Topical corticoids are the most effective treatment option for treating oral manifestations of GVHD.

2.3. Objectives

Main objectives

- To investigate different topical treatment options available for oGVHD

Secondary objectives

- To know the most effective option available according to scientific evidence
- To investigate the best time span of administration of the different topical agents
- To evaluate possible side effects related to the topical treatment agents

3. MATERIALS AND METHODS

3.1. Protocol development

A systematic review protocol was developed following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement explained in table A1 (Annex) (43).

3.2. Eligibility criteria

3.2.1. PICO question identification

The Population, Intervention, Comparison, and Outcome (PICO) framework was used to ask the following question: "What is the most effective topical treatment of oral graft-versus-host disease in hematopoietic stem cell transplant recipients?", as further explained in table 3.

Table 3:PICO framework applied to phrase the research question.

P	**I**	**C**	**O**
Population	*Intervention*	*Comparison*	*Outcome*
Clinical trials carried out on patients who received a HSCT and developed GVHD.	Local treatment of oral lesions associated to graft-versus-host disease.	Different topical treatment agents like steroidal and non-steroidal agents in different presentations as cremes, gel, spray, mouthwash, etc.	Efficacy of different local treatment options in oral graft-versus-host disease and their relationship with treatment prognosis and possible side effects.

3.2.2. Establishment of inclusion and exclusion criteria

<u>The inclusion criteria were</u>

- Randomized controlled trials (RCTs) between 2011-2022
- Languages: English, German, Spanish
- Studies performed on humans

- Studies with clear descriptions of the topical therapy used and its method of application

The exclusion criteria were

- Studies with less than 10 participants
- Studies focusing on prophylactic measures of oGVHD
- Studies which also included the treatment of extraoral manifestations
- Studies evaluating the effectiveness of systemic treatment of GVHD
- Studies addressing the treatment of secondary effects deriving from radio-/ chemotherapy

3.3. Information sources and search strategy

An electronic search of four databases (Medline Complete, PubMed, Scopus, and Cochrane Library) was carried out to identify possibly relevant studies. There was a language restriction of English, Spanish, and German and the period covered was from January 2011 until March 2022.

The following search strategy was carried out, using the operators "AND" and "OR" and the following keywords: ("Graft vs Host Reaction" OR "Graft vs Host Disease" OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "Chronic oral graft versus host disease") AND ("Topical" OR "Local treatment" OR "Oral" OR "Mouthwash" OR "Buccal" OR "Topical treatment" OR "Topical corticosteroids" OR "Topical administration" OR "Spray" OR "Gel" OR "Topical therapy").

The latest update on PubMed, Scopus, and Cochrane Library was undertaken the 2nd of March 2022, whereas for Medline Complete it was carried out the 3rd of March 2022. Also, the manual search was carried out, checking the references of selected studies.

In table 4, the different data bases used, the search strategy and filters applied, as well as the date of the search and the number of articles obtained, are depicted.

Table 4: Description of data bases used, search strategy, applied filters, date of search, and number of articles obtained.

Data bases	Search	Filters	Date	Number of articles
Scopus	("Graft vs Host Reaction" OR "Graft vs Host Disease" OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "chronic oral graft versus host disease") - *Article title* AND ("Topical" OR "local treatment" OR "Oral" OR "mouthwash" OR "Buccal" OR "Topical treatment" OR "Topical corticosteroids" OR "Topical administration" OR "Spray" OR "Gel" OR "Topical therapy") - *Article title/ abstract/ keywords*	Publication year: 2011-2022 Language: English, Spanish, German Type of source: Articles	02.03.2022	320
PubMed	("Graft vs Host Reaction" [Mesh] OR "Graft vs Host Disease" [Mesh] OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "chronic oral graft versus host disease") – *title* AND ("Topical" OR "local treatment" OR "Oral" OR "mouthwash" OR "Buccal" OR "Topical treatment" [Mesh] OR "Topical corticosteroids" OR "Topical administration" OR "Spray" OR "Gel" OR "Topical therapy") – *title abstract*	Publication year: 2011-2022 Language: German, English, Spanish Type of trials: Clinical trials, randomized controlled trial Species: Humans	02.03.2022	91
Cochrane Library	((MeSH descriptor: [Graft vs Host Reaction] explode all trees) OR (MeSH descriptor: [Graft vs Host Disease] explode all trees) OR (("Graft vs Host Reaction" OR "Graft vs Host Disease" OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "chronic oral graft versus host disease")): ti,ab,kw) AND ((MeSH descriptor: [Administration, Topical] explode all trees) OR ("Topical" OR "local treatment" OR "Oral" OR "mouthwash" OR "Buccal" OR "Topical treatment" OR "Topical corticosteroids" OR "Topical administration" OR "Spray" OR "Gel" OR "Topical therapy"))	Publication year: 2011-2022 Language: English, German, Spanish	02.03.2022	263
Medline complete	((MH "Graft vs Host Reaction+") OR (MH "Graft vs Host Disease") OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "chronic oral graft versus host disease") – *title* AND ("Topical" OR "Local treatment" OR "Oral" OR "Mouthwash" OR "Buccal" OR "Topical treatment" OR "Topical corticosteroids" OR (MH "Administration, Topical+") OR "Spray" OR "Gel" OR "Topical therapy") – *abstract*	Publication year: 2011-2022 Language: English, German, Spanish Species: Humans Type of trial: Adaptive clinical trial, case reports, clinical study, clinical trial, comparative study, controlled clinical trial, evaluation study, journal article, multicenter study, observational study, randomized controlled trial	03.02.2022	415

3.4. Study selection process and data collection

Titles were downloaded into Mendeley software (Elsevier Inc, NY, USA) to manage bibliographic references. The publication data (journal, volume number, page, and

year), title and abstract of all studies identified in the primary and secondary searches were compared and duplicate records were eliminated.

Titles and abstracts were independently reviewed by two blind reviewers (L.H., M.C.P.). If there was not sufficient information provided in the abstract or in case of disagreement regarding inclusion, the full article was reviewed by the reviewers and discrepancy was resolved by mutual consensus of all reviewers.

3.5. Data extraction

A spreadsheet (Excel 2021; Microsoft, Redmond, Washington, USA) was used to extract data from the included articles. The following data were collected: Article characteristics (article title, authors, publication year, type of study) and study characteristics (country of study, study design, period of intervention, topical agent, mode of application, intervention group, control group, population age/ gender, diagnosis tool used, data collection/ analysis, outcomes, side effects). The data was summarized in smaller tables.

3.6. Bias evaluation

The quality of the included clinical studies was evaluated by a reviewer (L.H.) following the Critical Appraisal Skills Program (CASP) Randomized Controlled Trial Standard checklist (44). The tool is composed of four sections and a total of 11 questions. Section A is composed of three questions which are evaluating the validity of the study design of the clinical trial. Section B is comprised of three questions focusing on the methodology of the studies, whereas section C refers to the results. Section D refers to the applicability of the outcomes to the local population. There are three different answer options available ranging from positive affirmation to uncertainty to negation.

4. RESULTS

The search strategy generated a total of 1089 articles (Figure 1). After the exclusion of 346 duplicates, 743 articles were identified as eligible records for screening. However, after scanning the articles' title, 649 were excluded, whilst 94 article abstracts were scanned. After reading the abstracts, 76 articles were excluded, and 18 records were sought for retrieval. Out of the 18 articles, 4 full articles could not be retrieved as they were studies currently being carried out without published results. 9 articles were excluded: 4 articles which were not RCTs or did not explain the methodology sufficiently, 3 articles which were duplicates but appeared under different names in the databases, and 2 which were not found relevant for the objective of this systematic review. Further data is shown in table 5. 5 RCTs were included in this systematic review which were published between January 2011 and March 2022 and fit the inclusion criteria stated above.

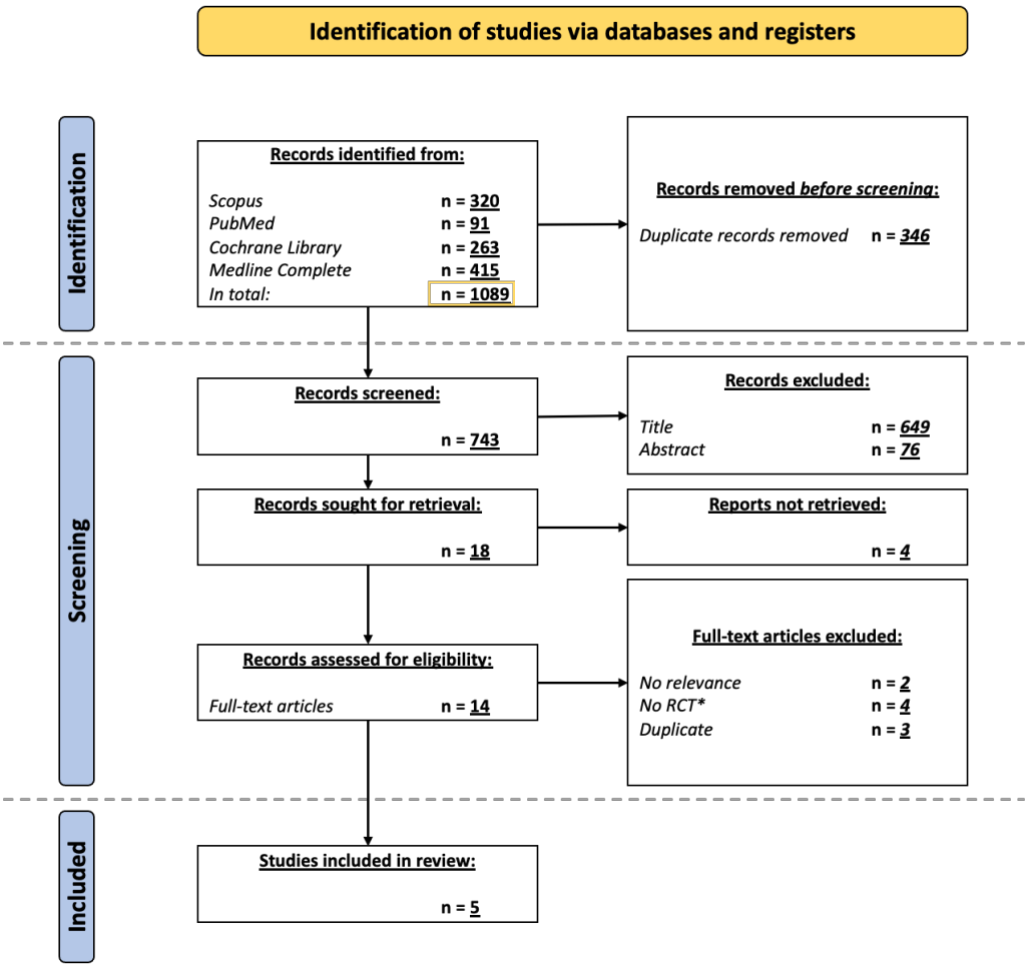

Figure 1: Flow-chart of the search carried out in the four databases.

Table 5: Exclusion of articles after full text analysis.

Authors	Name of the article	Reason of exclusion
Markiewicz *et al.* (45) 2012	Treating oral mucositis with a supersaturated calcium phosphate rinse: comparison with control in patients undergoing allogeneic hematopoietic stem cell transplantation	Not relevant
Park *et al.* (46) 2013	Comparison of budesonide and dexamethasone for local treatment of oral chronic graft-versus-host disease	Prospective cohort study, no RCT
St John *et al.* (47) 2013	Topical thalidomide gel in oral chronic GVHD and role of in situ cytokine expression in monitoring biological activity	Not relevant
Noce *et al.* (48) 2014	Topical clobetasol and dexametasone for oral chronic graft-vs-host disease	Duplicate of Noce, *et al.* (48)
Noce *et al.* (48) 2014	Clinical Trial With Clobetasol and Dexamethasone for Topical Treatment of Oral Lesions of Chronic Graft-versus-host Disease	Duplicate of Noce, *et al.* (48)
Picardi *et al.* (49) 2017	Therapeutic efficiency of platelet gel for the treatment of oral ulcers related to chronic graft versus host disease after allogeneic haematopoietic stem cell transplantation	Clinical study, no RCT
Bojanic *et al.* (40) 2018	Autologous blood as a source of platelet gel for the effective and safe treatment of oral chronic graft-versus-host disease	Clinical study, no RCT
Treister *et al.* (50) 2020	Topical sirolimus for management of refractory oral chronic graft-versus-host disease	Lack of methodology description
Pavletic *et al.* (51)	A Randomized Double-Blind Pilot Study of Topical Clobetasol 0.05% Oral rinse for Oral Chronic Graft-Versus-Host Disease	Duplicate of "Clobetasol for Oral Graft-Versus-Host Disease" by Pavletic *et al.* which was not available as article

4.1. Analysis of the studies characteristics

The five RCTs included were two Randomized Double-Blind Clinical Trial (48,52), an Open, Randomized, Multicenter Trial (53), an Open-Label Phase II Randomized Trial (54), and a Randomized Clinical Trial (55). Table 6 gives further information about the characteristics of each study.

In tables A2 and A3 (Annex), the studies and patients' characteristics are described. They were published between 2012 and 2019, involving a total of 157 patients of which 140 were evaluated at baseline and at the end of the study. The studies were carried out in Germany/ Israel, Brazil, United States of America, Iran, and Italy. The mean age of the participants varied from 35.8 to 62.5 and the sex ratio was male dominant (48,52–55).

Oral manifestations involved in cGVHD were erythema, atrophy, ulcer, lichen, hyperkeratosis, pseudomembrane, edema and mucocele, appearing as a mucus cyst on the soft palate, on the labial and buccal mucosa, and xerostomia (48,52–55).

Oral manifestations linked to GVHD diagnosis was done on different parameters across the included studies: World Health Organization (WHO) toxicity oral/ gastrointestinal, modified Oral Mucosal Rating Scale (mOMRS), Oral Mucositis Assessment Scale (OMAS), NIH oral cavity severity score, mucosal score, and oral

symptoms score, Dry Mouth Questionnaire (DMQ), sialometry, various Visual Analogue Scales (VAS), and biopsies (48,52–55).

Table 6: Characteristics of the included RCTs.

Author/ Country/ Year	Type of study	Population size	Length of study
Elad *et al.* (53) **Germany, Israel** **2012**	Open, Randomized, Multicenter Trial	19 patients were screened, 18 were included	8 weeks
Noce *et al.* (48) **Brazil** **2014**	Randomized Double-Blind Clinical Trial	35 were recruited, 32 were included, 28 were evaluated	4 weeks
Treister *et al.*(54) **USA** **2016**	Prospective, Single-center, Open-Label, Randomized Phase II Trial	46 were enrolled, 6 were excluded from analysis	4 weeks
Mansourian *et al.* (55) **Iran** **2017**	Randomized Clinical Trial	26	4 weeks
Bardellini *et al.* (52) **Italy** **2019**	Randomized Double-Blind Clinical Trial	31 were recruited, 28 were included	2 weeks

4.2. Evaluation of risk of bias

Overall, two RCTs were considered at certain risk of bias because of the missing blinding of study participants and investigators (53,54). Further data is described in tables 7 and 8.

Table 7: Risk of bias for the RCTs following CASP checklist.

Section/ Questions		Elad *et al.* (53) **2012**	Noce *et al.* (48) **2014**	Treister *et al.* (54) **2016**	Mansourian *et al.* (55) **2017**	Bardellini *et al.* (52) **2019**
Section A Is the basic study design valid for a randomized controlled trial?	Did the study address a clearly focused research question?	Yes	Yes	Yes	Yes	Yes
	Was the assignment of participants to interventions randomized?	Yes	Yes	Yes	Yes	Yes
	Were all participants who entered the study accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
Section B Was the study methodologically sound?	Were the participants 'blind' to intervention they were given? Were the investigators 'blind' to the intervention they were giving to participants? Were the people assessing/analyzing outcome/s 'blinded'?	No, no, can't tell	Yes, yes, can't tell	No, no, can't tell	Yes, yes, can't tell	Yes, yes, can't tell
	Were the study groups similar at the start of the randomized controlled trial?	Yes	Yes	Yes	Yes	Yes

	Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	Yes	Yes	Yes	Yes	Yes
Section C What are the results?	Were the effects of intervention reported comprehensively?	Yes	Yes	Yes	Yes	Yes
	Was the precision of the estimate of the intervention or treatment effect reported?	Yes	Yes	Yes	Yes	Yes
	Do the benefits of the experimental intervention outweigh the harms and costs?	Yes	Yes	Yes	Yes	Yes
Section D: Will the results help locally?	Can the results be applied to your local population/in your context?	Yes	Yes	Yes	Yes	Yes
	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?	Yes	Yes	Can't tell	Can't tell	Yes

Table 8: Risk of bias for the RCTs.

	Section A	Section B	Section C	Section D	Overall risk
Elad *et al.* (53) 2012	+	-	+	+	!
Noce *et al.* (48) 2014	+	+	+	+	+
Treister *et al.* (54) 2016	+	-	+	+	!
Mansourian *et al.* (55) 2017	+	+	+	+	+
Bardellini *et al.* (52) 2019	+	+	+	+	+

+	Low risk of bias
-	High risk of bias
!	Certain risk of bias

4.3. Synthesis of results

Topical treatment agents available for the treatment of oral GVHD

The different topical treatment options used in the studies included in this systematic review were topical dexamethasone, topical budesonide, malic acid, topical clobetasol, topical tacrolimus, triamcinolone in orabase, and curcumin in orabase. An overall of 44 patients received dexamethasone, 18 patients received topical budesonide, 14 patients received malic acid, 14 patients a placebo, 14 patients received clobetasol, 14 patients received tacrolimus, 13 patients received triamcinolone in orabase, and 13 patients received curcumin in orabase (48,52–55).

Most effective topical treatment option available

Clinical response to these agents were 61% for WHO toxicity oral/gastrointestinal, 26.7-61% for mOMRS, 69% for OMAS, 14-50% for NIH oral cavity response, and an increase of 0-9-1.1mL/min of the unstimulated salivary flow rate (SFR) (48,52–55).

Elad *et al.* (53) observed relative median reduction in the mOMRS of 70%, a median relative reduction of 69% in the OMAS, 61% for the WHO toxicity scale gastrointestinal/ oral. The rate of objective response which was defined as more than 50% compared to baseline using the mOMRS was not significantly different among the 4 study arms.

In the study of Noce *et al*. (48) there was a reduction of 3.0 (53.9% of cases) in the mOMRS, reduction of 2.1cm in the VAS symptomatic response, reduction of 0.10cm in the VAS xerostomia score, and an increase of 0.11mL/min of resting SFR in the clobetasol group. For the dexamethasone group, reduction of 1.0 (26.7% of cases) in the mOMRS, reduction of 1.4cm in the VAS symptomatic response, and a reduction of 1.75cm in the VAS xerostomia could be observed. The median reduction in mOMRS total score was significantly higher in the clobetasol group than the reduction observed in the dexamethasone group (p=0.03). Also, the median reduction in the symptomatic response (VAS) was significantly better for the clobetasol group than for the dexamethasone group (p=0.02). However, the median VAS xerostomia scores were significantly improved in patients in the dexamethasone group (p=0.04) but not in the clobetasol group (p=0.06). A significant increase in the median SFR in the clobetasol

group was noted (p=0.01) but no significant differences in SFR were observed in the dexamethasone group (p=1.00).

In the study conducted by Treister *et al*. (54), for the dexamethasone group a sensitivity response in 58% was observed. 69% achieved an overall response. The OMS response was 8%, and the NIH Oral Cavity Severity Score response 50%. The tacrolimus arm was closed early due to a lack of activity in the sensitivity response with 21% only. Overall response was observed in 50%, 36% in the OMS response, and 14% responded to the NIH Oral Cavity Severity Score response.

Mansourian *et al.* (55) observed a mean severity reduction of $4.11 \pm 1.04 mm^2$ in the curcumin group and a reduction of 1.93 ± 0.37 in the VAS pain severity at day 14, and 3.77 ± 0.66 at day 28. In the triamcinolone control group, mean severity reduction was $4.23 \pm 1.49 mm^2$. Reduction of 2.15 ± 0.14 at day 14 according to the VAS pain severity was stated, and a reduction of 4.46 ± 0.37 at day 28. There was no significant difference of the alleviated severity between the two groups (p=0.052). Also, the severity of the pain at the baseline (p=0.287), day 14 (p=0.362), and day 28 (p=0.687) was not significantly different between the two groups.

In the study conducted by Bardellini *et al.* (52) the DMQ scores increased by 2.2 points. The unstimulated SFR increased by 0.09 ± 0.02mL/min. A significant increase of $p<0.05$ was observed in the DMQ scores, as well as in the SFR with $p<0.05$.

Further significance considerations are described in table A4 (Annex).

Because of the heterogeneity of the studies, direct comparisons of the outcomes could not be drawn between all the studies.

Table 9 compares the differences of unstimulated SFR at baseline and the endpoint of the studies. The highest increase of SFR could be observed in clobetasol, followed by malic acid, and dexamethasone.

Table 9: Unstimulated SFR in comparison.

Topical agent	Baseline	End of study
Malic acid	0.15 ± 0.06 mL/min	0.24± 0.08
Clobetasol	0.19 (0.02-1.6) mL/min	0.30 mL/min
Dexamethasone	0.24 (0.02-0.84) mL/min	No significant difference (p=1.00)

As described in table 10, the highest treatment response according to the mOMRS was observed in budesonide with 61% of the patients, followed by clobetasol with 53.9% of the patients, and dexamethasone with 26.7% of the patients showing treatment response.

Table 10: Treatment responses according to the mOMRS.

Topical agent:	**Number of patients improved (%) at final evaluation:**
Budesonide	61
Clobetasol	53.9
Dexamethasone	26.7

Figure 2 represents the overall response between three studies. The blue bars refer to the number of patients participating in the trial and the red bars refer to the number of patients that responded to the treatment.

For the study carried out by Elad *et al.* (53), the improvement of 50% of the mOMRS was defined as objective response, for Noce *et al.* (48) the symptomatic response was taken into consideration, and for Treister *et al.* (54) the overall response described by the authors was used. According to the results, the best overall response is present for the budesonide regardless of the different application regimens, followed by clobetasol, and dexamethasone.

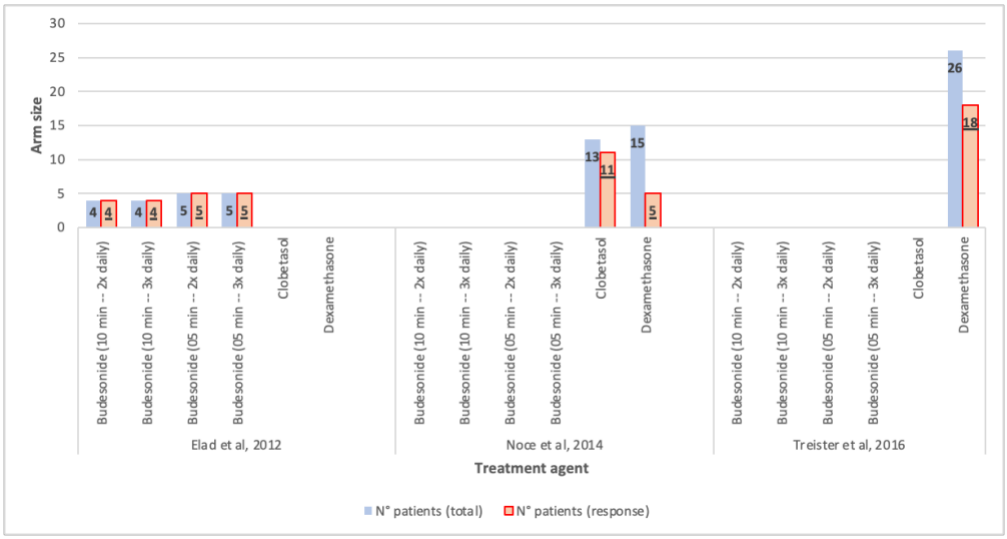

Figure 2: Comparison of overall response between patients receiving budesonide, clobetasol, and dexamethasone.

Best time span of administration of the different topical agents

The studies evaluated were held in a period of 2 to 8 weeks with a median range of 4.4 weeks (48,52–55).

As described in table 11, in the study carried out by Elad *et al.* (53), the rate of objective response using the mOMRS was not significantly different among the 4 study arms over a period of 8 weeks. They included 5 evaluations in their study: day 0, day 14, day 28, day 42, day 56 with a window of $\pm$ 4 days. The mean duration of treatment for reaching the best oral cGVHD status ranged between 5.28 and 6.50 weeks for their 4 scales used: time to lowest mOMRS score, time to lowest OMAS score, time to lowest WHO toxicity gastrointestinal/ oral score, and time to lowest oral cGVHD 5-level score. The only scale showing significant differences between the arm regarding the response to treatment was "time to minimal WHO toxicity gastrointestinal/ oral score" (p=0.0265).

In the study conducted by Noce *et al.* (48), when applying clobetasol for 28 days, significant increase of SFRs was observed, whereas no significant differences showed in the dexamethasone group. Median VAS xerostomia scores were significantly improved in patients in the dexamethasone group but not in the clobetasol group. Comparing clobetasol and dexamethasone over the 28-day span, the median reduction in mOMRS total score was significantly higher in the clobetasol group than the dexamethasone group. Also, the median reduction in the symptomatic response using VAS was significantly better for the clobetasol group.

In the study by Treister *et al*. (54), the tacrolimus arm was closed early due to a lack of activity with only 21% of the patients showing a sensitivity response rate improvement. The dexamethasone group had a sensitivity response in 58% of the patients over a period of 4 weeks.

Mansourian *et al*. (55) observed that there was a mean severity reduction of $4.11\pm1.04mm^2$ in the curcumin group and a mean severity reduction of $4.23\pm1.49mm^2$ in the triamcinolone group with no significant difference of the alleviated severity between the two groups (p=0.052) over a period of 4 weeks. They included an interim evaluation at day 14 showing a VAS pain severity reduction of 1.93 ± 0.37 in the case group and 2.15 ± 0.14 in the control group. At day 28 the reduction was 3.77 ± 0.66 for

the curcumin group and 4.46±0.37 for the triamcinolone group. The severity of the pain at the baseline (P=0.287), day 14 (P=0.362), and day 28 (P=0.687) was not significantly different between the two groups.

Bardellini *et al.* (52) administered malic acid over a period of 2 weeks to treat GVHD-induced xerostomia. Significant increases of the DMQ and unstimulated SFRs were observed.

Table 11: Response rates according to the period of administration.

Author/ Country/ Year	**Treatment agent**	**Length of study**	**Response**
Elad *et al.* (53) **Germany, Israel 2012**	Budesonide	8 weeks	mOMRS: Median relative reduction of 70% OMAS: Median relative reduction of 69% WHO toxicity scale gastrointestinal/ oral: Reduction of at least I step 61%
Noce *et al.* (48,54) **Brazil 2014**	Clobetasol, Dexamethasone	4 weeks	Clobetasol: mOMRS: Reduction of 3.0 (53.9% of cases) VAS symptomatic response: Reduction of 2.1cm VAS xerostomia: Reduction of 0.10cm SFR: Increase of 0.11mL/min Dexamethasone*:* mOMRS: Reduction of 1.0 (26.7% of cases) VAS symptomatic response: Reduction of 1.4cm VAS xerostomia: Reduction of 1.75cm SFR: -
Treister *et al.* (54,55) **USA 2016**	Dexamethasone, Tacrolimus	4 weeks	Dexamethasone: Sensitivity response: in 58% Overall response: in 69% OMS response: 8% NIH Oral Cavity Severity Score response: 50% Tacrolimus: Sensitivity response: in 21% Overall response: in 50% OMS response: 36% NIH Oral Cavity Severity Score response: 14%
Mansourian *et al.* (55) **Iran 2017**	Curcumin in orabase, Triamcinolone in orabase	4 weeks	Curcumin: Mean severity provided by NIH scale for oGVHD: Reduction of 4.11±1.04mm^2 VAS pain severity day 14: Reduction of 1.93±0.37 VAS pain severity day 28: 3.77±0.66 Triamcinolone: Mean severity provided by NIH scale for oGVHD: Reduction of 4.23±1.49mm^2 VAS pain severity day 14: Reduction of 2.15±0.14 VAS pain severity day 28: Reduction of 4.46±0.37
Bardellini *et al.* (52) **Italy 2019**	Malic acid	2 weeks	DMQ scores: Increase of 2.2 points Unstimulated SFR: Increase of 0.09 ± 0.02 mL/min

Possible side effects of the topical treatment agents

Reported adverse effects were gastrointestinal disorders, such as cheilitis and esophagitis, fungal infections, such as candidiasis, and nervous system disorders like

taste alterations and burning sensations, and oral cavity pain (48,52–55). Additional data is described in Table 12.

Table 12: Side effects possibly related to topical treatment agents.

Author/ Country/ Year	Topical agent	N° of patients evaluated	N° of patients affected/ Side effects
Elad *et al.* (53) **Germany, Israel 2012**	Budesonide	18	8 patients had adverse events: 6 mild, 2 moderate events including: gastrointestinal disorders (cheilitis, esophagitis), fungal infection, and nervous system disorder (taste alteration).
Noce *et al.* (48) **Brazil 2014**	Group A: Topical clobetasol Group B: Dexamethasone	Group A: 14 Group B: 18	Group A: 1 patient with burning sensation. Group B: 1 patient with burning sensation who discontinued the topical treatment.
Treister *et al.* (54) **USA 2016**	Group A: Topical dexamethasone Group B: Tacrolimus oral solution	Group A: 26 Group B: 14	Group A: There was one report of oral cavity pain. Group B: One subject developed candidiasis.

Table 13 gives information on the percentage of patients that developed side effects in relation to the topical agent administered. Most adverse effect could be seen in the treatment with budesonide, where 44.4% of the patients referred to side effects (53). 7.14% of the patients treated with clobetasol and 7.14% of the patients treated with tacrolimus solution developed adverse effects (48,54). Only 4.55% of the patients treated with topical dexamethasone reported side effects (48).

Table 13: Percentages of adverse effect regarding the topical treatment.

Topical agent	Percentages of patients presenting adverse events
Budesonide	44.4%
Clobetasol	7.14%
Tacrolimus	7.14%
Dexamethasone	4.55%

Figure 3 shows the number of patients referring to adverse effects in relation to the number of patients evaluated.

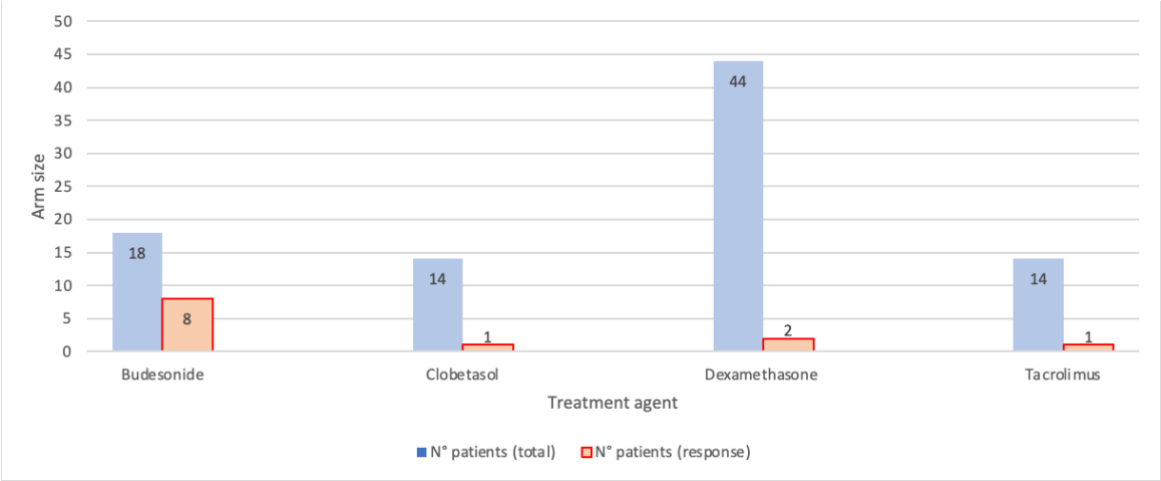

Figure 3: Diagram of adverse effects.

5. DISCUSSION

There are a few systematic reviews assessing the different topical agents for the treatment of oral GVHD (39,56,57).

Albuquerque *et al.* (56) conducted a systematic review on the management of oral GVHD which was published in 2016. They stated that there is a limited number of RCTs available that investigate the topical treatment options for oral lesions linked to GVHD. 7 studies were analyzed, of which 2 were RCTs and 5 were cohort studies. They emphasized the need of high quality RCTs investigating the efficacy of treatment of oral GVHD to establish clinical guidelines.

Elsaadany *et al.* (57) included 6 clinical trials focusing on the topical treatment with corticosteroids. Those were 2 RCTs, 3 cohort studies, and 1 before and after clinical trial. According to their results, clobetasol, followed by budesonide showed promising clinical efficacy. However, based on the lack of RCTs, judging the efficacy and safety of the topical agents was a major limitation according to the authors.

Sava *et al* (39) carried out a systematic review on the topical treatment of oral manifestations of GVHD, focusing on topical corticosteroids only, due to the lack of RCTs carried out on alternative agents. According to their results, budesonide, followed by clobetasol, and dexamethasone showed the highest overall response. However, they also concluded that more RCTs with larger cohorts are needed to assess the effectiveness of topical treatment agent.

In this systematic review, 5 RCTs were included, most of which had a small population size. It was evident, that there is a great degree of heterogeneity within the studies.

Bardellini *et al.* (52) focused on the treatment of GVHD-induced xerostomia of HSCT recipients. Xerostomia and hypo-salivation were determined at the baseline of the study by evaluating the DMQ scores and unstimulated salivary flow rate using sialometry. Both, patients with subjective complaint of dry mouth and objective hypo-salivation, were included into their study. The 28 participants were divided into two groups of 14 participants, of which one group received 1% malic acid and the other a placebo over a period of 14 days. At the end of the study, patients were again assessed using the DMQ

and sialometry to evaluate the unstimulated SFR. According to their results, both DMQ scores as well as unstimulated SFR increased significantly in the group receiving malic acid compared to the group receiving a placebo.

Malic acid shows some advantages over other topical treatment options tested in the past. Citric acid has been previously studied as topical sialagogue, however, due to its demineralizing effects on human dentin and subsequently increased risk of caries, its use has been repudiated (58). Most of the products containing high doses of acidic components are mainly associated with chewable consumption, which prolongs the contact of the product with the tooth surface and thus enhances the erosive action. Malic acid's mechanism of action is linked to the dissociation of H^+ in malic acid in water which becomes hydronium ions and therefore generating a stimulation of salivary secretion to dilute the concentration of acids in the oral cavity (59). However, as SalivAktive® contains xylitol, the erosive action and the cariogenic potential are counteracted.

There are systemic treatment options available to treat drug-induced xerostomia, like pilocarpine and cevimeline. However, they have been linked to side effects, such as excessive sweating, cutaneous vasodilation, gastro-intestinal disturbances, persistent hiccups, bronchoconstriction, hypotension, bradycardia, increased urinary frequency, and vision problems (60). Therefore, the need of further investigating topical therapeutical alternatives is clearly indicated to avoid adverse effects of systemic treatment.

However, there are some limitations within this study. Their study period of 14 days, as well as the population size of 28 participants is rather small, indicating the necessity of carrying out further RCTs on larger population sizes to confirm their result of malic acid being a valid option as a salivary stimulant for the treatment of cGVHD-induced xerostomia. Furthermore, patients with subjective sensation of dry mouth as well as patients with objective hypo-salivation were included in the study, however, it was not clearly indicated in their materials and methods section which patient showed what characteristic. In future investigations, it might be interesting to evaluate the effectiveness of malic acid in patients complaining of xerostomia versus patients diagnosed with hypo-salivation.

In their study, the sole treatment of xerostomia was investigated which is why the conclusion, that malic acid is an effective topical treatment option of oral manifested GVHD, cannot been assumed. However, it seems to be a valid alternative for the topical treatment of GVHD-induced xerostomia.

Noce *et al.* (48) compared two topical corticosteroids, clobetasol and dexamethasone, in a population sized 14 and 18 correspondingly over a period of 28 days. For the final evaluation only 28 patients were evaluated. They hypothesized that clobetasol provided a better response than dexamethasone in the treatment of oral lesions of cGVHD. Oral lesions were evaluated using the mOMRS and symptoms were registered using the VAS. In the clobetasol group, there was a significant reduction in the mOMRS total score. In the dexamethasone and clobetasol group, there was a significant difference of symptomatic improvement, however, the clobetasol's one was greater. With the finalization of the RCT, they concluded that topical clobetasol and dexamethasone were efficacious in the alleviation of oral cGVHD, however, clobetasol proved to be more effective in the symptomatic and the morphologic improvement.

Their main limitation was the small population size which exposed their analysis to the presence of confounding variables, like immunosuppressive treatment, duration of topical therapy, and salivary flow rates. Furthermore, their patients included had experienced long intervals after their HSCT intervention, letting to the assumption that most of their participants reflect "difficult-to-treat cGVHD" and have higher frequency of systemic disorders. Added to that, the response rates to the treatment were analyzed at a specific point in time. A "time to event" analysis might offer a greater insight into the impact of the stated agents.

There are not many studies carried out comparing the effectiveness of clobetasol or dexamethasone in the treatment of oral GVHD. When comparing the two agents in the treatment of oral lichen planus, topical clobetasol has proven to be more effective (61,62). In a study conducted by Wolff *et al*. (63) dexamethasone had a high response of 68.75% when used as topical treatment of oral GVHD. However, their participants received the topical agent up until 9 months. In the study carried out by Noce *et al.* (48), the intervention period was only 28 days. Therefore, it can be hypothesized that

prolonged topical application may improve response outcomes. However, there are no studies carried out investigating this possible correlation.

Elad *et al.* (53) conducted a multicenter study with four treatment arms to investigate the rate of objective response of patients with oral cGVHD to various dosing protocols of a new topical budesonide formulation. The patients received 3mg budesonide effervescent tablets dissolved in 10mL of water either twice or three times a day during 5 or 10 minutes of application.

The 18 participants were split into four groups with different dosages of budesonide and different duration of administration. Randomization was provided, however, neither the analyzed population, nor the personnel were blinded. The study period consisted of 8 weeks with 5 evaluations overall. Patients between 18 and 75 years of age were included showing symptomatic oral cGVHD of erosive and ulcerative type. Patients were excluded if they presented oral cGVHD of hyperkeratotic type only, presented active bacterial, viral, or fungal infections, required an additional systemic therapy, or had received any second-line treatment of oral cGVHD with topical steroids within 12 weeks before the start of the trial.

Severity of oral involvement was evaluated using the mOMRS, oral cGVHD 5-level scale, WHO toxicity scale gastrointestinal/ oral, and OMAS. “Objective response” was defined as an improvement of at least 50% at the final visit in comparison to the baseline evaluation in the mOMRS.

According to their results, there were no significant differences in response rate among the four treatment arms. All patients showed improvement, and more than half improved objectively. Greatest improvement was noted after 5 to 7 weeks of treatment. According to their safety analysis, a dosing schedule of 3 mg of budesonide 3 times a day applied for 10 minutes in the form of a mouthwash is supported.

Adverse effects possibly related to the study drug appeared in half the patients, however they were only mild to moderate and most of them resolved with the cessation of the study drug.

In previously carried out trials, the dose of topical budesonide for the treatment of oral cGVHD was higher than the dose described in this study (64,65). Regardless of the

administration time, all studies had favorable outcomes. To avoid patient incompliance, the application time in this study was reduced.

One of the study's limitations is the small patient size of 18 participants only. However, there is a larger Double-blind Randomized, Placebo-controlled Multicenter Phase III Clinical Study carried out on 186 patients based on the study of Elad *et al.* (53) to determine the efficacy and tolerability of budesonide 3mg effervescent tablet (9mg/ day) compared to placebo for the treatment of patients with resistant oral cGVHD. Another possible limitation could be the patient compliance as the intense application regimen states that the agent must be applied up to 30 minutes a day. However, according to the authors, patient compliance was not described as problematic either in their study or in previous studies (64,65).

Another limiting factor is the non-blinding of participants and personnel, giving rise to bias when it comes to evaluation of the results. However, the primary purpose of this study was to investigate the objective response of patients with oral cGVHD to various dosing protocols which included different time spans and thus making it difficult to blind participants. In their currently carried out large-scale, phase III, Randomized, Controlled, Double-Blinded Study in multiple centers, the efficacy of this safe dose of the new preparation of topical budesonide in the treatment of oral cGVHD is being assessed where double-blinding is provided.

Treister *et al.* (54) assessed the efficacy and toxicity of topical dexamethasone and tacrolimus solutions in treating oral cGVHD over a period of 4 weeks. 46 patients were enrolled, 6 were excluded, 28 patients received dexamethasone solution, and 18 patients received tacrolimus solution. Adult patients and pediatric patients $\geq$4 years old with new onset symptomatic oral cGVHD were included after having received allo-HCT. Systemic immunosuppressive regimens had to be stable for four weeks prior to study entry. Exclusion criteria was previous treatment with intraoral topical corticosteroids and/ or tacrolimus therapy.

The participants were evaluated at baseline and after four weeks of treatment which included clinician-assessed instruments like the NIH oral cavity severity score and the NIH oral mucosal score. Patient-assessed instruments included NIH oral symptom scores

and questions referring to oral intake limitations related to the symptoms. A 0-10 numerical scale was used to determine the overall response.

The study showed that topical dexamethasone 0.1 mg/mL solution, when rinsed for one month intensively three to four times a day for 5 minutes, is safe and effective at reducing the symptoms of oral cGVHD. Tacrolimus 0.1 mg/mL solution, even though it is safe and well-tolerated, seemed to be less effective. The tacrolimus arm was closed early after an interim analysis was performed and only 3 patients met the response criteria.

Most patients did not report discomfort associated with the drug administration. There was one case of oral cavity pain associated to dexamethasone use. One patient receiving tacrolimus developed candidiasis, and one subject who was priorly diagnosed with buccal squamous cell carcinoma that at the baseline visit was not sufficiently distinct from the surrounding cGVHD changes, became evident at the final visit. However, the case of buccal squamous cell carcinoma was not considered as related to the study treatment.

According to their results, it was concluded that dexamethasone 0.1 mg/mL solution can be considered as first-line topical therapy, and as the comparator for future trials of novel strategies. Furthermore, higher concentrations of topical tacrolimus should be evaluated in future studies.

One of their major limitations was the lack of blinding of patients and practitioners giving rise to bias when evaluating the response outcomes. Added to that, the short study intervention span of 4 weeks, and the rather small sample size were also limiting factors. Furthermore, the tacrolimus arm was closed early due to a lack of efficacy, even though almost 75% of the patients reported symptomatic improvement of treatment. It was assumed that this could be due to the low concentration of tacrolimus used in this study. Therefore, it was suggested to carry out clinical trials testing higher concentrations of tacrolimus.

Effectiveness of topical tacrolimus has been assessed in several case reports and series, however, there is no larger sample size RCT. Mawardi *et al.* (66) for instance, reported that there was a synergistic effect when combined with topical steroids, however, it was not proven to be effective when administered on its own.

Mansourian *et al.* (55) conducted a RCT to compare the efficacy of topical curcumin in orabase and triamcinolone in orabase in the patients affected by oral GVHD. 26 patients were divided into two groups of 13 patients each, using block randomization. The study lasted 28 days and patients were evaluated at baseline, after 28 days, as well as weekly assessments. Patients presenting oral GVHD for at least three months without systemic medication for the treatment of the oral lesions were included into the study. The clinician was blinded to the group allocation. A VAS score was used to assess the level of pain severity and severity of the lesions was assessed using the GVHD scoring introduced by the NIH.

The mean severity of oral mucosal involvement improved in the case group receiving curcumin, as well as in the control group receiving triamcinolone without any significance difference between both groups. Also, the severity of pain at baseline and 28 days afterwards was not significant different between the two groups. Therefore, the authors concluded that curcumin in orabase has comparable efficacy to triamcinolone in orabase when treating oral manifestations linked to cGVHD.

In their RCT, an alternative treatment option to corticosteroids is evaluated and compared to the efficacy of the corticosteroid triamcinolone. Curcumin has long been used in traditional medicine for wound healing and pain relief. Recent studies have shown that it decreases the levels of TNF-α, IL-1β and IFN-γ cytokines and thus exerts anti-inflammatory and antioxidative effects (67). Furthermore, it has been related to antibacterial, antifungal, antiviral, and disinfecting properties. Fungal infections, alterations in the oral microbial flora, and increased TNF and IL levels are related to the aggravation of oral lesions in GVHD (68). Therefore, decreasing those levels is a desirable effect for a topical therapeutical and justifies their intent of evaluating the efficacy of curcumin as topical treatment option for oral cGVHD. However, according to Mansourian *et al.* (55), their RCT is the first study carried out to investigate curcumin's efficacy in patients suffering from oral GVHD. Therefore, it is difficult to draw direct conclusions. There is a lack of larger carried out RCTs to strengthen their thesis.

The study has some limitations. Firstly, they carried out the trial on a small sample size over a short period of time of 28 days only. Furthermore, little information was provided on patient characteristics and oral involvement at baseline and after the trial.

Added to that, they did not provide information on how many patients in total showed response to the treatment and if there were patients who did not show response at all.

It is difficult to draw direct comparison of all the RCTs used in this systematic review. Different assessment tools were used, the time span of the studies varied, as well as the sample sizes. Oral GVHD is a complex disease and expressing itself in more than just one oral manifestation.

Most effective topical treatment option

Regarding the treatment of GVHD-induced xerostomia, Bardellini *et al.* (52) stated a significant increase in the DMQ score when using malic acid as topical treatment. In the study carried out by Noce *et al.* (48) it could be observed that there was a significant improvement in the median VAS xerostomia, whereas there was no significant difference for the clobetasol group. However, when looking at the unstimulated SFR it was observed that there was no significant increase in patients treated with dexamethasone, whereas in the clobetasol there was a significant increase. Also, in the study of Bardellini *et al.* (52) there was a significant increase in SFR. According to the authors, the increase of resting SFR when applying clobetasol was rather unexpected. Further research is needed to investigate the efficacy of topical therapy on the salivary glands affected by cGVHD. From the results obtained in this systematic review it can be hypothesized that malic acid is the more effective topical treatment of treating GVHD-induced xerostomia as improvements could be observed in the subjective improvement as well as in unstimulated SFRs. However, more studies on bigger cohorts over a longer period must be carried out to prove that thesis.

Regarding the treatment of oral manifestations of GVHD as a whole and not just treating xerostomia, it is difficult to determine which of the topical agents the most effective option is.

When comparing the response rates on the mOMRS, budesonide caused the highest response regardless of the different arms, followed by clobetasol, and dexamethasone. The tacrolimus arm of Treister *et al.* (54) was closed early due to lack of activity in the sensitivity response, which is why its results were not considered relevant in this systematic review. For curcumin in orabase and triamcinolone in orabase, the

percentages of participants that improved overall response were not stated. However, in both groups, severity of oral involvement, as well as pain severity improved with no significant difference between both groups (55). This leads to the conclusion that curcumin in orabase shows similar efficacy as triamcinolone in orabase. However, due to the low number of participants enrolled in this study, further research is needed to manifest this thesis.

Treatment span

According to the 5 evaluation points of Elad *et al.* (53) the mean duration of topical treatment with budesonide for reaching the best oral cGVHD status ranged between 5.28 and 6.50 weeks for their 4 scales used.

Using clobetasol for 4 weeks showed significant greater magnitudes and rates of response compared to dexamethasone and tacrolimus, which was terminated earlier due to lack of activity. According to Noce *et al.* (48) the study period of 4 weeks might have been too short. When comparing their results to a previous conducted study, differences in response outcome as well as in application period was observed. In the study by Wolff *et al.* (63) for instance, a morphological response of 68.75% was reported with application duration varying between 12 days to 9 months. This leads to the assumption that prolonged treatment periods might be necessary. However, Treister *et al.* (54) stated that 1 month is a sufficient duration of therapy for evaluation of response of dexamethasone but due to their short follow-up period, durability of the response was not evaluated. This leads to the conclusion that already after 4 weeks improvement can be observed, however, to achieve an increase in overall response rates, the treatment period might need to be expanded.

Comparing the efficacy of curcumin in orabase to triamcinolone in orabase over a period of 4 weeks showed similar results, both of which are promising (55).

Also, malic acid over a span of 2 weeks showed an improvement in the subjective and objective symptoms (52).

Adverse effects

Budesonide is not only linked to the highest treatment overall response rates, but also showed the most adverse effects (53). However, none of them were considered

severe. It also must be taken into consideration, that the side effects reported, such as affectation of the GI tract, fungal infections, etc., are also common characteristics of complications of GVHD (27,69). Therefore, those findings must be interpreted with caution, as they might or might not be related to the administration of the topical therapeutical. Furthermore, Bardellini *et al.* (52) did not give any information on possible side effects leading to the assumption, that no unpleasant events were reported, however, a long-term follow-up study would be interesting, investigating the effect of malic acid on the dental enamel, since it has been linked to erosive capacity in previous studies.

Limitations

Limitations of this review include the use of four databases only during the search: PubMed, Medline complete, Scopus, and Cochrane. Added to that, articles published in English, German, and Spanish language were reviewed only, leading to a possible exclusion of other relevant data.

Furthermore, the low number of RCTs included in this review represents a major limitation when it comes to drawing conclusion on the efficacy of topical treatment on oral GVHD.

Added to that, the heterogeneity of the oral assessment tools used for baseline evaluation and after therapy made it difficult to draw direct comparisons between the studies.

Furthermore, objective outcome was defined by the author (L.H.) to be able to compare the studies' overall response. This bears high risk of misinterpretation of the studies' results, as well as bias.

Future aspirations

It is evident that there is still a lack of research regarding the most effective topical treatment for the oral manifestations of GVHD. In the future, larger RCTs should be carried out with a bigger patient cohort and over a longer period. In addition, various parameters should be considered, such as the pharmaceuticals used as systemic treatment, patients' underlying diseases, and conditioning regimens, which might alter or influence the response to the topical treatment. Also, the studies should be following

similar study designs to allow better comparison, taking into consideration the time of intervention, as well as the assessment tools used for diagnosing and final evaluation.

Furthermore, there is a need for standardization of systemic treatment regimen for HSCT-recipients, diagnostic methods, assessment tools for GVHD, and first-line topical therapy for the treatment of oGVHD.

6. CONCLUSION

- The different topical treatment options analyzed in this systematic review were dexamethasone, budesonide, malic acid, clobetasol, tacrolimus, triamcinolone, and curcumin.
- According to the overall response rates of topical treatment of oral GVHD, budesonide showed the most promising results, followed by clobetasol, and dexamethasone. Malic acid seemed to be the most effective option in the treatment of GVHD-induced xerostomia.
- The average time span of treatment administration was 4.4 weeks. Almost all studies concluded the necessity of further research investigating the possible increase of effectiveness of the agents when applied over a longer period of time.
- Commonly reported side effects were gastrointestinal disorders, fungal infections, and nervous system disorders. Most adverse effects were associated to budesonide use.

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ANNEX

Table A- 1: PRISMA guideline.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	V
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	18
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	18
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	20
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	21-22
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	21-22
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	22-23
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	22-23
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	-
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	-
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	23
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	-
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	25
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	26
Study characteristics	17	Cite each included study and present its characteristics.	27
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	27-28
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	31-35, Annex 54-57
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	37
	23b	Discuss any limitations of the evidence included in the review.	46-47
	23c	Discuss any limitations of the review processes used.	37-44
	23d	Discuss implications of the results for practice, policy, and future research.	47
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

Table A- 2: Characteristics of the included RCTs.

Author/ Country/ Year	Population size	Oral assessment at baseline	Topical agent	Length of study	Assessment tool	Clinical response	Outcome
Elad *et al.* (53) **Germany, Israel 2012**	19 patients were screened, 18 were included	Arm A: mOMRS: 34 (23-40) WHO toxicity scale GI/ O: Grade 2: 100% OMAS: 2.0 (1.7-2.0) Arm B: mOMRS: 37 (21-63) WHO toxicity scale GI/ O: Grade 2: 60%; Grade 3: 40% OMAS: 2.6 (1.0-4.0) Arm C: mOMRS: 25 (23-26) WHO toxicity scale GI/ O: Grade 1: 25%, Grade 2: 75% OMAS: 1.8 (0.7-2.0) Arm D: mOMRS: 24 (20-44) WHO toxicity scale GI/ O: Grade 1: 20%; Grade 2: 60%; Grade 3: 20% OMAS: 1.1 (0.7-2.1)	3mg budesonide effervescent tablet dissolved in 10 mL of water: Arm A: 10 minutes 3 times daily Arm B: 5 minutes 3 times daily Arm C: 10 minutes 2 times daily Arm D: 5 minutes 2 times daily	8 weeks	Assessment of severity of oral cGVHD using the: mOMRS, WHO toxicity scale GI/ O, and OMAS	Arm A: mOMRS (number of patients with objective response): 50% WHO toxicity scale GI/ O (number of patients with reduction): 25% OMAS (number of patients with any reduction): 100% Arm B: mOMRS (number of patients with objective response): 40% WHO toxicity scale GI/ O (number of patients with reduction): 60% OMAS (number of patients with any reduction): 100% Arm C: mOMRS (number of patients with objective response): 75% WHO toxicity scale GI/ O (number of patients with reduction): 75% OMAS (number of patients with any reduction): 100% Arm D: mOMRS (number of patients with objective response): 80% WHO toxicity scale GI/ O (number of patients with reduction): 80% OMAS (number of patients with any reduction): 100% Total: mOMRS median relative reduction: 61%; WHO toxicity scale GI/O: 61%; OMAS: 100%	Topical budesonide mouthwash improved oral lesions linked to GVHD. There were no significant differences in response rate among the 4 treatment arms.
Noce *et al.* (48) **Brazil 2014**	35 were recruited, 32 were included,	Group A: VAS for sensitivity of oral lesions: 4.25 (1.7-10.0) cm	Group A: Topical clobetasol	28 days	mOMRS for the grading of oral lesions. VAS for	Group A: VAS symptomatic response (TR + PR): 11 patients	There was significant symptomatic improvement in both groups, but clobetasol was significantly more effective

	28 were evaluated	VAS for xerostomia: 4.10 (0.0-10.0) cm Resting SFR: 0.19 (0.02-1.6) mL/min <u>Group B:</u> VAS for sensitivity of oral lesions: 5.00 (1.4-9.7) cm VAS for xerostomia: 5.15 (0.2-9.0) cm Resting SFR: 0.24 (0.02-0.84) mL/min	propionate 0.05% <u>Group B:</u> Dexamethasone 0.1mg/ ml		symptomatic response. Sialometry for determining SFR to evaluate oral dryness.	mOMRS: improved in 53.9% VAS for sensitivity of oral lesions: reduction of 2.1 cm → 2.15cm VAS for xerostomia: 4.00 cm Resting SFR: 0.30 mL/min <u>Group B:</u> VAS symptomatic response (TR + PR: 5 patients mOMRS: improved in 26.7% VAS for sensitivity of oral lesions: reduction of 1.4 cm → 3.6cm VAS for xerostomia: 3.40 cm Resting SFR: no significant difference (p=1.00)	than dexamethasone for the amelioration of symptoms and clinical aspects of oral lesions in cGVHD.
Treister *et al.* (54) **USA** **2016**	46 were enrolled, 6 were excluded from analysis	Oral cGVHD NIH oral cavity severity score, NIH oral mucosal score, NIH oral symptom scores, oral biopsies.	<u>Group A:</u> Topical dexamethasone 0.5 mg/5 mL <u>Group B:</u> Tacrolimus oral solutions 0.5 mg/5 mL	4 weeks	Extent, severity, and clinical impact of oral cGVHD was evaluated via NIH oral cavity severity score and NIH oral mucosal score. NIH oral symptom score was used as patient-based assessment.	<u>Group A:</u> Sensitivity response: 58% Overall response: 69% Oral mucosal score response: PR: 8%; NR: 88%; PD: 4%; NIH Oral Cavity Score Response: 50% <u>Group B:</u> Sensitivity response: 21% Overall response: 50% Oral mucosal score response: PR: 36%; NR: 64%; PD: 0%; NIH Oral Cavity Score Response: 14%	Topical dexamethasone 0.1 mg/mL solution is safe and effective at reducing the symptoms of oral cGVHD. Tacrolimus 0.1 mg/mL solution appeared less effective when applied in the same fashion.
Mansouria n *et al.* (55) **Iran** **2017**	26	<u>Group A:</u> Mean severity: 9.69±2.65mm^2 Mean pain score: 5.62±1.80 <u>Group B:</u> Mean severity: 8.54±2.43mm^2 Mean pain score: 6.46±1.89	<u>Group A:</u> Curcumin in orabase <u>Group B:</u> Triamcinolone in orabase	28 days	The GVHD scoring provided by the NIH was used to assess the severity of the lesions. VAS was used to assess the level of the pain severity.	<u>Group A:</u> Mean severity: 5.54±1.61mm^2 Mean pain score: 1.85±1.14 <u>Group B:</u> Mean severity: 4.31±0.94mm^2 Mean pain score: 2±1.52	Curcumin in orabase has comparable efficacy to that of triamcinolone in orabase and may be beneficial for the treatment of the patients presenting with oral GVHD.
Bardellini *et al.* (52) **Italy** **2019**	31 were recruited, 28 were included	<u>Group A:</u> DMQ scores: 1.3 ± 0.4 Unstimulated SFR: 0.15 ± 0.06 mL/min <u>Group B:</u> DMQ scores: 1.2 ± 0.7 Unstimulated SFR: 0.16 ± 0.07 mL/min	<u>Group A:</u> Topical sialagogue spray containing malic acid 1% (Salivaktive®) <u>Group B:</u> Placebo	2 weeks	DMQ to assess severity of dry mouth. Sialometry to evaluate the unstimulated SFR.	<u>Group A:</u> DMQ scores: 3.5 ± 0.4 (p<0.05) Unstimulated SFR: 0.24± 0.08 mL/min <u>Group B:</u> DMQ scores: 1.4 ± 0.6 (p>0.05) Unstimulated SFR: 0.17 ± 0.09 mL/min (p>0.05)	There was an increase of the unstimulated salivary flow rate, after the use of 1% malic acid spray for 2 weeks. 1% malic acid as a salivary stimulant can be a valid option for the treatment of cGVHD-induced xerostomia.

**DMQ: Dry Mouth Questionnaire, *SFR: Salivary Flow Rate, *VAS: Visual Analogue Scale, *mOMRS: Modified Oral Mucositis Rating Scale, *WHO toxicity O/ GI: World Health Organization toxicity oral/ gastrointestinal, *OMAS: Oral Mucositis Assessment Scale, *TR: Total remission, *PR: Partial response, *NR: No response, *PD: Progressive disease;*

Table A- 3: Characteristics of the included RCTs.

Author/ Country/ Year	Underlying disease	Age (years) (median/ mean)	Population gender	Side effects
Elad *et al.* (53) **Germany, Israel 2012**		Arm A: Mean (SD), years: 35.8 (8.4) Median (range), years: 36.0 (26-45) Arm B: Mean (SD), years: 44.6 (9.6) Median (range), years: 45.0 (34-55) Arm C: Mean (SD), years: 53.3 (14.2) Median (range), years: 57.0 (33-66) Arm D: Mean (SD), years: 42.0 (8.2) Median (range), years: 40.0 (34-55)	Arm A: Male: 4 Female: 0 Arm B: Male: 4 Female: 1 Arm C: Male: 3 Female: 1 Arm D: Male: 2 Female: 3	Eight patients had adverse events: 6 mild, 2 moderate events including: gastrointestinal disorders (cheilitis, esophagitis), fungal infection, and nervous system disorder (taste alteration).
Noce *et al.* (48) **Brazil 2014**	Group A: Chronic myeloid leukemia: 4 Acute myeloid leukemia: 6 Acute lymphocytic leukemia: 1 Hodgkin lymphoma: 1 Chronic lymphocytic leukemia: 1 Non-Hodgkin lymphoma: 1 Myelofibrosis: 1 Multiple myeloma: 1 Aplastic anemia: 1 Myelodysplastic syndrome: 1 Group B: Chronic myeloid leukemia: 5 Acute myeloid leukemia: 2 Acute lymphocytic leukemia: 2 Hodgkin lymphoma: 2 Chronic lymphocytic leukemia: 1 Non-Hodgkin lymphoma: 1 Myelofibrosis: 1	Group A: 45.50 (27-66) Group B: 53.00 (29-60)	Group A: Male: 6 Female: 18 Group B: Male: 8 Female: 10	Group A: 1 patient with burning sensation. Group B: 1 patient with burning sensation who discontinued the topical treatment.
Treister *et al.* (54) **USA 2016**	Group A: Acute myelogenous leukemia: 9 Non-Hodgkin lymphoma: 6 Acute lymphoblastic lymphoma: 4 CLL/ Small lymphocytic lymphoma/ Prolymphocytic leukemia: 3 Chronic myelogenous leukemia: 2 Myelodysplastic syndrome: 1 Hodgkin disease: 1 Group B: Acute myelogenous leukemia: 6 Non-Hodgkin lymphoma: 1 Acute lymphoblastic lymphoma: 1 CLL/ Small lymphocytic lymphoma/ Prolymphocytic leukemia: 3 Chronic myelogenous leukemia: 1 Myelodysplastic syndrome: 2 Hodgkin disease: 0	Group A: 55 (29-70) Group B: 62.5 (24-75)	Group A: Male: 10 Female: 16 Group B: Male: 10 Female: 4	Group A: There was one report of oral cavity pain. Group B: One subject developed candidiasis.
Mansourian *et al.* (55) **Iran 2017**	Group A: Acute myeloid leukemia: 9 Acute lymphoblastic leukemia: 2 Multiple myeloma: 2 Hodgkin's lymphoma: 0 Group B: Acute myeloid leukemia: 7 Acute lymphoblastic leukemia: 2 Multiple myeloma: 3 Hodgkin's lymphoma: 2	Group A: 35.23±7.67 Group B: 39.15±12.13	Group A: Male: 8 Female: 5 Group B: Male: 7 Female: 6	No significant side effects were stated even at high doses.
Bardellini *et al.* (52)		Group A: 45+7.8	Group A: Male: 11	None stated.

Italy 2019		Group B: 42+7.3	Female: 3 Group B: Male: 8 Female: 6	

Table A- 4: Treatment response and corresponding significance consideration.

Author/ Country/ Year	Treatment agent	Response	Significance consideration
Elad *et al.* (53) **Germany, Israel 2012**	Budesonide	mOMRS: Median relative reduction of 70% OMAS: Median relative reduction of 69% WHO toxicity scale gastrointestinal/ oral: Reduction of at least I step 61%	Rate of objective response (more than 50% compared to baseline) using the mOMRS was not significantly different among the 4 study arms. The only scale that showed significant differences between the study arms regarding the response to treatment was ''time to minimal WHO toxicity gastrointestinal/oral score'': Arm A: 8.08 weeks, Arm B: 4.02 weeks, Arm C: 7.90 weeks, Arm D: 4.42 weeks (p=0.0265).
Noce *et al.* (48) **Brazil 2014**	Clobetasol, Dexamethasone	Clobetasol: mOMRS: Reduction of 3.0 (53.9% of cases) VAS symptomatic response: Reduction of 2.1cm VAS xerostomia: Reduction of 0.10cm SFR: Increase of 0.11mL/min Dexamethasone: mOMRS: Reduction of 1.0 (26.7% of cases) VAS symptomatic response: Reduction of 1.4cm VAS xerostomia: Reduction of 1.75cm SFR: -	Median reduction in mOMRS total score was significantly higher in the clobetasol group than the reduction observed in the dexamethasone group (p=0.03). Median reduction in the symptomatic response (VAS) was significantly better for the clobetasol group than for the dexamethasone group (p=0.02). Median VAS xerostomia scores were significantly improved in patients in the dexamethasone group (p=0.04) but not in the clobetasol group (p=0.06). A significant increase in the median SFR in the clobetasol group was noted (p=0.01). No significant differences in SFR were observed in the dexamethasone group (p=1.00).
Treister *et al.* (54) **USA 2016**	Dexamethasone, Tacrolimus	Dexamethasone: Sensitivity response: in 58% Overall response: in 69% OMS response: 8% NIH Oral Cavity Severity Score response: 50% Tacrolimus: Sensitivity response: in 21% Overall response: in 50% OMS response: 36% NIH Oral Cavity Severity Score response: 14%	26 subjects in the dexamethasone arm completed both study visits and were included in the response analysis, 58% with response rate, compared with 21% in the tacrolimus arm (*P* = .05). The response rates according to the NIH score in the dexamethasone and tacrolimus arms were 50% and 2%, respectively (*P* = .04).
Mansourian *et al.* (55) **Iran 2017**	Curcumin in orabase, Triamcinolone in orabase	Curcumin: Mean severity provided by NIH scale for oGVHD: Reduction of 4.11±1.04mm^2 VAS pain severity day 14: Reduction of 1.93±0.37 VAS pain severity day 28: 3.77±0.66 Triamcinolone: Mean severity provided by NIH scale for oGVHD: Reduction of 4.23±1.49mm^2 VAS pain severity day 14: Reduction of 2.15±0.14 VAS pain severity day 28: Reduction of 4.46±0.37	No significant difference of the alleviated severity between the two groups (p=0.052). The severity of the pain at the baseline (P=0.287), day 14 (P=0.362), and day 28 (P=0.687) was not significantly different between the two groups.
Bardellini *et al.* (52) **Italy 2019**	Malic acid	DMQ scores increased by 2.2 points. Unstimulated SFR increased by 0.09 ± 0.02 mL/min.	DMQ score: Significant increase (p<0.05) SFR: Significant increase (p<0.05)

Topical treatment of oral chronic graft-versus-host- disease in hematopoietic stem cell transplant recipients: A Systematic Review

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Keywords: *Hematopoietic stem cell transplant, oral graft-versus-host disease, topical treatment.*

Background: Oral graft-versus-host disease (GVHD) is a common complication of hematopoietic stem cell transplantation. This study systematically reviewed Randomized Controlled Trials (RCTs) with the objective to investigate the effectiveness and side effects of topical agents used for the treatment of oral GVHD.

Materials and Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed to perform this study. An electronic search of three databases was conducted. RCTs published between January 2011 and March 2022 were included that were carried out on hematopoietic stem cell transplant recipients receiving topical treatment for oral GVHD. The Critical Appraisal Skills Program (CASP) standard checklist for RCTs was used for the bias risk evaluation.

Results: Five RCTs were included for the qualitative synthesis of results. Two RCTs were linked to a certain risk of bias. Budesonide caused the highest overall treatment response. Malic acid, clobetasol, and dexamethasone increased resting salivary flow rates. Curcumin in orabase showed similar results to corticosteroid treatment. Adverse effects were observed in populations receiving budesonide, dexamethasone, clobetasol, and tacrolimus. Most frequent adverse effects were burning sensations, fungal infections, and gastrointestinal disorders, but none of them were severe.

Conclusion: Given the small number of RCTs performed and the heterogeneity of the different study designs, it is difficult to draw direct comparisons. Malic acid appears to be effective for the treatment of graft-versus-host disease-induced xerostomia. Budesonide had the highest

overall response rates but was also associated with the highest number of adverse effects. Further research is needed to manifest those findings.

Introduction: Hematopoietic stem cells are multipotent cells and are responsible for the generation of all functional hematopoietic lineages (1). Hematopoietic stem cell transplants (HSCTs) aim to counteract problems related to the inappropriate functioning of the hematopoietic system, like hematologic malignancies, select solid tumors, nonmalignant conditions, and severe immunologic deficiencies (1–4). The rationale of HSCTs is to achieve a broad lymphoablation that allows an initial breakdown of the immunological memory repertoire. As a result, the hematopoietic and thus the immune system is regenerated, which enables an immunological renewal (3). Due to the severe immunosuppression, as well as the rigorous conditioning regimen applied in oncologic patients, the patients might suffer severe complications (5). The major lethal complication of HSCT is graft-versus-host disease (GVHD), an immunological disorder in which the donor's lymphocytes attack the healthy recipient's tissues (5–7). GVHD is a multisystemic disorder affecting several organs. The skin is the main manifestations site, however many manifestations present itself in the oral cavity (5,7–9). Common oral manifestations include erythema, erosions, ulcers, lichenoid lesions, xerostomia, and pain (8,10). In some cases, mucoceles and mucosal atrophy have also been observed (7). The first-line therapy for GVHD are systemic corticosteroids. However, due to their associated secondary effects like osteoporosis and avascular necrosis, topical alternatives are under current investigation (10,11). For oral GVHD, common corticosteroid solutions or gels are dexamethasone, budesonide, clobetasol, prednisolone, and triamcinolone (10,12,13). Another alternative under current investigation is gel rich in platelets (14,15). A non-steroidal option includes tacrolimus (12,16). Non-pharmacological options comprise different types of phototherapies, like psoralen ultraviolet-A, UV-B therapy, photobiomodulation therapy, and carbon dioxide laser therapy (12,17,18). Even though there are many options available, there is still no consensus on the most effective option available, nor standardized guidelines. This review aims to provide a systematic approach of literature including RCTs investigating the efficacy and possible side effects of topical agents used for the treatment of oral GVHD.

Material and Methods:

- **Protocol and focused question:**

A systematic review was conducted including RCTs to compare different topical treatment agents. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed (19). The following question was developed according to the population, intervention, comparison, and outcome study design. What is the most effective topical treatment for oral graft-versus-host disease in hematopoietic stem cell transplant recipients?

- **Selection criteria:**

Only RCTs published between January 2011 and March 2022 in languages English, German, or Spanish were included. The studies had to be performed in vivo on humans with clear description of the topical therapy used and its method of application. Studies comprised of less than 10 participants, studies focusing on prophylactic measures or systemic treatment of oral GVHD, and studies including the treatment of extra-oral manifestations were excluded.

- **Search strategy:**

An electronic search was conducted in MEDLINE via PubMed, Scopus, and Cochrane Central Register of Controlled Trials. The following Medical Subject Heading (MeSH) and text words were used: ("Graft vs Host Reaction" OR "Graft vs Host Disease" OR "GVHD" OR "Graft-versus-host disease" OR "Graft versus host disease" OR "Graft-versus-host reaction" OR "Chronic oral graft versus host disease") and combined with the Boolean term "AND" ("Topical" OR "Local treatment" OR "Oral" OR "Mouthwash" OR "Buccal" OR "Topical treatment" OR "Topical corticosteroids" OR "Topical administration" OR "Spray" OR "Gel" OR "Topical therapy"). Manual search of reference list was performed to identify additional articles.

- **Screening methods and data abstraction:**

Two independent reviewers (LH and MCP) performed the search. After removal of duplicates, the titles and abstracts were scanned for eligibility. Full text analysis was performed of the articles considered eligible and inclusion and exclusion criteria were applied. In case of disagreement regarding inclusion, discrepancy was resolved by mutual consensus of all reviewers. The following data was extracted: author, year of publication, country, study type,

sample size, population gender and age, manifestations at baseline, treatment design, length of study, treatment response, and side effects.

- **Risk of bias:**

The Critical Appraisal Skills Program (CASP) standard checklist for RCTs was used to evaluate the potential risk of bias (20). The checklist is comprised of four segments referring to basic study design, methodology, results, and discussion. These segments were evaluated by two reviewers (LH and MCP) and an overall assessment of risk of bias was performed ranging from low, high, or certain risk of bias.

Results:

- **Study selection:**

From the 1089 studies retrieved during the search, 14 were considered eligible and according to the inclusion and exclusion criteria, a total of 5 studies were included: two Randomized Double-Blind Clinical Trial (21,22), an Open, Randomized, Multicenter Trial (23), an Open-Label Phase II Randomized Trial (24), and a Randomized Clinical Trial (25). Figure 1 shows the identification, screening, and inclusion of the studies included in this systematic review.

- **Characteristics of included studies:**

The studies were published between 2012 and 2019, involving a total of 157 patients of which 140 were evaluated at baseline and at the end of the study. The studies were carried out in Germany/ Israel, Brazil, United States of America, Iran, and Italy. The mean age of the participants varied from 35.8 to 62.5 and the sex ratio was male dominant. Further characteristics are shown in table 1. Oral manifestations involved in cGVHD were erythema, atrophy, ulcer, lichen, hyperkeratosis, pseudomembrane, edema and mucocele, appearing as a mucus cyst on the soft palate, on the labial and buccal mucosa, and xerostomia. Oral manifestations linked to GVHD diagnosis was done on different parameters across the included studies: World Health Organization (WHO) toxicity oral/ gastrointestinal, modified Oral Mucosal Rating Scale (mOMRS), Oral Mucositis Assessment Scale (OMAS), NIH oral cavity severity score, mucosal score, and oral symptoms score, Dry Mouth Questionnaire (DMQ), sialometry, various Visual Analogue Scales (VAS), and biopsies (21–25).

- **Risk of bias:**

Figure 2 shows the estimated risk of bias. Two studies were considered at certain risk of bias due to the missing of blinding of patients and interventionists (23,24).

- **Synthesis of the results:**

The different topical therapeutics used in the studies included were, topical dexamethasone, topical budesonide, malic acid, topical clobetasol, topical tacrolimus, triamcinolone in orabase, and curcumin in orabase. Elad *et al.* (23) observed relative median reduction in the mOMRS of 70%, a median relative reduction of 69% in the OMAS, 61% for the WHO toxicity scale gastrointestinal/ oral. The rate of objective response which was defined as more than 50% compared to baseline using the mOMRS was not significantly different among the 4 study arms. In the study of Noce *et al*. (21) there was a reduction of 3.0 (53.9% of cases) in the mOMRS, reduction of 2.1cm in the VAS symptomatic response, reduction of 0.10cm in the VAS xerostomia score, and an increase of 0.11mL/min of resting SFR in the clobetasol group. For the dexamethasone group, reduction of 1.0 (26.7% of cases) in the mOMRS, reduction of 1.4cm in the VAS symptomatic response, and a reduction of 1.75cm in the VAS xerostomia could be observed. The median reduction in mOMRS total score was significantly higher in the clobetasol group than the reduction observed in the dexamethasone group (p=0.03). Also, the median reduction in the symptomatic response (VAS) was significantly better for the clobetasol group than for the dexamethasone group (p=0.02). The median VAS xerostomia scores were significantly improved in patients in the dexamethasone group (p=0.04) but not in the clobetasol group (p=0.06). A significant increase in the median SFR in the clobetasol group was noted (p=0.01) but no significant differences in SFR were observed in the dexamethasone group (p=1.00). In the study conducted by Treister *et al*. (24), for the dexamethasone group a sensitivity response in 58% was observed. 69% achieved an overall response. The OMS response was 8%, and the NIH Oral Cavity Severity Score response 50%. The tacrolimus arm was closed early due to a lack of activity in the sensitivity response with 21% only. Overall response was observed in 50%, 36% in the OMS response, and 14% responded to the NIH Oral Cavity Severity Score response. Mansourian *et al.* (25) observed a mean severity reduction of $4.11\pm1.04mm^2$ in the curcumin group and a reduction of 1.93±0.37 in the VAS pain severity at day 14, and 3.77±0.66 at day 28. In the triamcinolone control group, mean severity reduction

was 4.23±1.49mm^2. Reduction of 4.46±0.37 according to the VAS pain severity was stated at day 28. There was no significant difference of the alleviated severity between the two groups (p=0.052). Also, the severity of the pain at the baseline (p=0.287) and day 28 (p=0.687) was not significantly different between the two groups. In the study conducted by Bardellini *et al.* (22) the DMQ scores increased by 2.2 points. The unstimulated SFR increased by 0.09±0.02mL/min. A significant increase of $p<0.05$ was observed in the DMQ scores, as well as in the SFR with $p<0.05$. Table 2 shows the different unstimulated salivary flow rates pre- and post-intervention.

Figure 3 shows the overall response of patients receiving budesonide, clobetasol, and dexamethasone. For the study carried out by Elad *et al.* (23), the improvement of 50% of the mOMRS was defined as objective response, for Noce *et al.* (21) the symptomatic response was taken into consideration, and for Treister *et al.* (24) the overall response described by the authors was used.

Reported adverse effects were gastrointestinal disorders, such as cheilitis and esophagitis, fungal infections like candidiasis, and nervous system disorder like taste alterations, burning sensations and oral cavity pain (21–25). Additional data is described in Table 3. Most adverse effect could be seen in the treatment with budesonide, where 44.4% of the patients referred to side effects (23). 7.14% of the patients treated with clobetasol and 7.14% of the patients treated with tacrolimus solution developed adverse effects (21,24). Only 4.55% of the patients treated with topical dexamethasone reported side effects (21).

Discussion:

There are only a few systematic reviews assessing the different topical agents for the treatment of oral GVHD. Albuquerque *et al.* (26) conducted a systematic review published in 2016 analyzing seven studies, on the management of oral GVHD. They emphasized the need of high quality RCTs investigating the efficacy of treatment of oral GVHD to establish clinical guidelines. Elsaadany *et al.* (27) included six clinical trials focusing on the topical treatment with corticosteroids. According to their results, clobetasol, followed by budesonide showed promising clinical efficacy but due to the lack of RCTs, judging the efficacy and safety of the topical agents was a major limitation according to the authors. Sava *et al*. (28) carried out a

systematic review on the topical treatment of oral manifestations of GVHD, focusing on topical corticosteroids only due to the lack of RCTs carried out on alternative agents.

- **Most effective topical treatment:**

In this systematic review, 5 RCTs were included, most of which had a small population size. It was evident, that there is a great degree of heterogeneity within the studies. Regarding the treatment of GVHD-induced xerostomia, Bardellini *et al.* (22) stated a significant increase in the DMQ score and unstimulated salivary flow rate. Malic acid shows some advantages over other acids tested in the past. Citric acid has been previously studied as sialagogue, however, due to its demineralizing effects on human dentin and subsequently increased risk of caries, its use has been repudiated (29). Most of the products containing high doses of acidic components are mainly associated with chewable consumption, which prolongs the contact of the product with the tooth surface and thus enhances the erosive action. Malic acid's mechanism of action is linked to the dissociation of H+ in malic acid in water, hydronium ions formation and subsequent stimulation of salivary secretion aiding the dilution of acids in the oral cavity (30). Furthermore, the product tested by Bardellini *et al.* (22) contains xylitol, which counteracts the erosive action and the cariogenic potential. According to Noce *et al.* (21), the increase of resting SFR when applying clobetasol was rather unexpected. When comparing the overall response, the authors stated clobetasol was also more effective than dexamethasone which had a low response rate (21). In previous studies, when comparing the two agents in the treatment of oral lichen planus, topical clobetasol has also proven to be more effective (31,32). In a study conducted by Wolff *et al*. (33) dexamethasone had a high response of 68.75% when used as topical treatment of oral GVHD. However, their participants received the topical agent up until 9 months. When comparing the response rates on the mOMRS, budesonide caused the highest response regardless of the different arms, followed by clobetasol, and dexamethasone. This finding was also confirmed by Sava *et al.* (28). The tacrolimus arm of Treister *et al.* (24) was closed early due to lack of activity in the sensitivity response. Effectiveness of topical tacrolimus has been assessed in several case reports and series, however, there is no larger sample size RCTs. In a study conducted by Mawardi *et al.* (16), a synergistic effect when combined with topical steroids was observed, however, it was not proven to be effective when administered on its own. Mansourian *et al.* (25) stated that for curcumin and triamcinolone in

orabase, severity of oral involvement, as well as pain severity improved with no significant difference between both groups. Curcumin has long been used in traditional medicine for wound healing and pain relief. Recent studies have shown that it decreases the levels of TNF-α, IL-1β and IFN-γ cytokines and thus exerts anti-inflammatory and antioxidative effects (34). Furthermore, it has been related to antibacterial, antifungal, antiviral, and disinfecting properties, which might be beneficial in the treatment of oral lesions in GVHD (35). However, further research is needed to manifest that thesis.

- **Side effects:**

Regarding the side effects, budesonide appears to cause the most adverse effects (23). None of them were considered severe. It also must be taken into consideration, that the side effects reported, such as affectation of the gastro-intestinal tract, fungal infections, etc., are also common characteristics of complications of GVHD (5,36). Bardellini *et al.* (22) did not give any information on possible side effects leading to the assumption, that no unpleasant events were reported, however, a long-term follow-up study would be of interest, investigating the effect of malic acid on the dental enamel, as it was linked to erosive capacity in previous studies.
Limitations of this review include the use of four databases only during the search. Added to that, articles published in English, German, and Spanish language were reviewed only, leading to a possible exclusion of other relevant data. The low number of RCTs included in this review represents a major limitation when it comes to drawing conclusion on the efficacy of topical treatment on oral involvement of GVHD. Furthermore, an objective outcome was defined by the authors to compare the studies' overall response. This bears risk of misinterpretation of the studies' results, as well as bias.
In the future, more RCTs should be carried out with a larger number of participants and over a longer period. Various parameters should be considered, such as administered systemic treatment and conditioning regimen, and underlying diseases. Also, similar study designs would allow a better comparison between the studies, taking into consideration the time of intervention, as well as the assessment tools used for diagnosing and final evaluation. Furthermore, there is a need for standardization of systemic treatment regimen for HSCT-recipients, diagnostic methods, assessment tools for GVHD, and first-line topical therapy for the treatment of oral GVHD.

Conclusion:

To conclude budesonide showed the highest overall response, as well as the most adverse effects independently from the different administration protocols. Malic acid seems effective for the treatment of GVHD-induced xerostomia. More research is needed to manifest those findings.

Conflict of interest: The authors declare that they have no conflict of interests in this study. The study was designed, conducted, and analyzed by researchers belonging to the Universidad Europea de Valencia.

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Table 1: Characteristics of the included studies.

Author/ Country/ Year	Type of study	Population size	Length of study	Topical agent
Elad et al. (23)**, Germany/ Israel, 2012**	Open, Randomized, Multicenter Trial	19 patients were screened, 18 were included	8 weeks	3mg budesonide effervescent tablet dissolved in 10 mL of water Arm A: 10 minutes 3 times daily Arm B: 5 minutes 3 times daily Arm C: 10 minutes 2 times daily Arm D: 5 minutes 2 times daily
Noce et al. (21)**, Brazil, 2014**	Randomized Double-Blind Clinical Trial	35 were recruited, 32 were included, 28 were evaluated	4 weeks	Group A: Topical clobetasol propionate 0.05% Group B: Dexamethasone 0.1mg/ ml
Treister et al. (24)**, USA, 2016**	Prospective, Single-center, Open-Label, Randomized Phase II Trial	46 were enrolled, 40 were included	4 weeks	Group A: Topical dexamethasone 0.5 mg/5 mL Group B: Tacrolimus oral solutions 0.5 mg/5 mL
Mansourian et al. (25)**, Iran, 2017**	Randomized Clinical Trial	26 were included and evaluated	4 weeks	Group A: Curcumin in orabase Group B: Triamcinolone in orabase
Bardellini et al. (22)**, Italy, 2019**	Randomized Double-Blind Clinical Trial	31 were recruited, 28 were included	2 weeks	Group A: Topical sialagogue spray containing malic acid 1% (Salivaktive®) Group B: Placebo

Table 2: Unstimulated salivary flow rate in comparison.

Topical agent	Baseline	End of study
Malic acid	0.15 ± 0.06 mL/min	0.24± 0.08
Clobetasol	0.19 (0.02-1.6) mL/min	0.30 mL/min
Dexamethasone	0.24 (0.02-0.84) mL/min	No significant difference (p=1.00)

Table 3: List of reported adverse effects.

Author/ Country/ Year	Topical agent	N° of patients evaluated	N° of patients affected/ side effects
Elad *et al.* (23)**, Germany/ Israel, 2012**	Budesonide	18	8 patients had adverse events: 6 mild, 2 moderate events including: gastrointestinal disorders (cheilitis, esophagitis), fungal infection, and nervous system disorder (taste alteration).
Noce *et al.* (21)**, Brazil, 2014**	Group A: Clobetasol Group B: Dexamethasone	Group A: 14 Group B: 18	Group A: 1 patient with burning sensation. Group B: 1 patient with burning sensation who discontinued the topical treatment.
Treister *et al.* (24)**, USA, 2016**	Group A: Dexamethasone Group B: Tacrolimus	Group A: 26 Group B: 14	Group A: 1 report of oral cavity pain. Group B: 1 patient developed candidiasis.

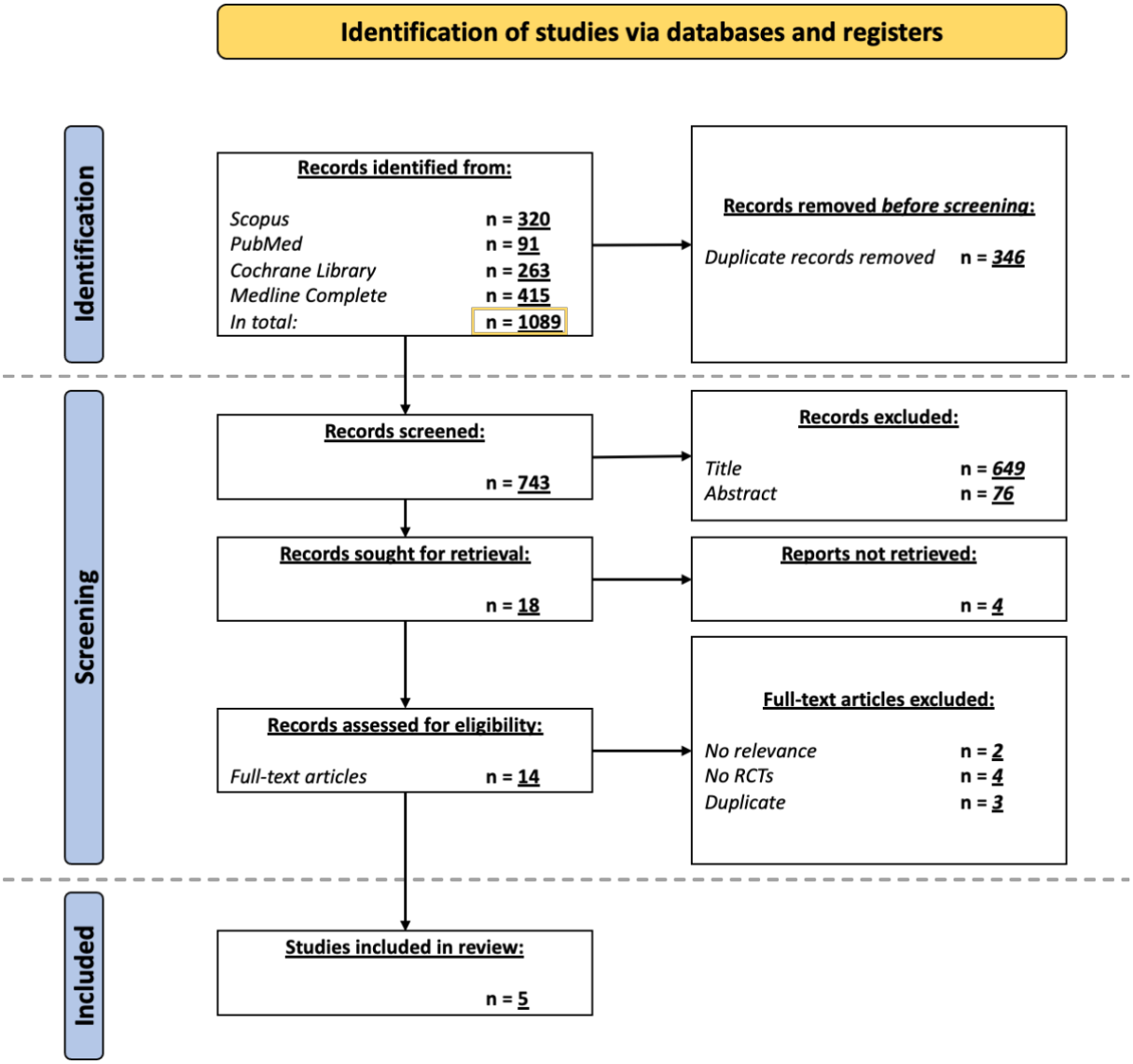

Figure 1: Flow-chart of the search carried out.

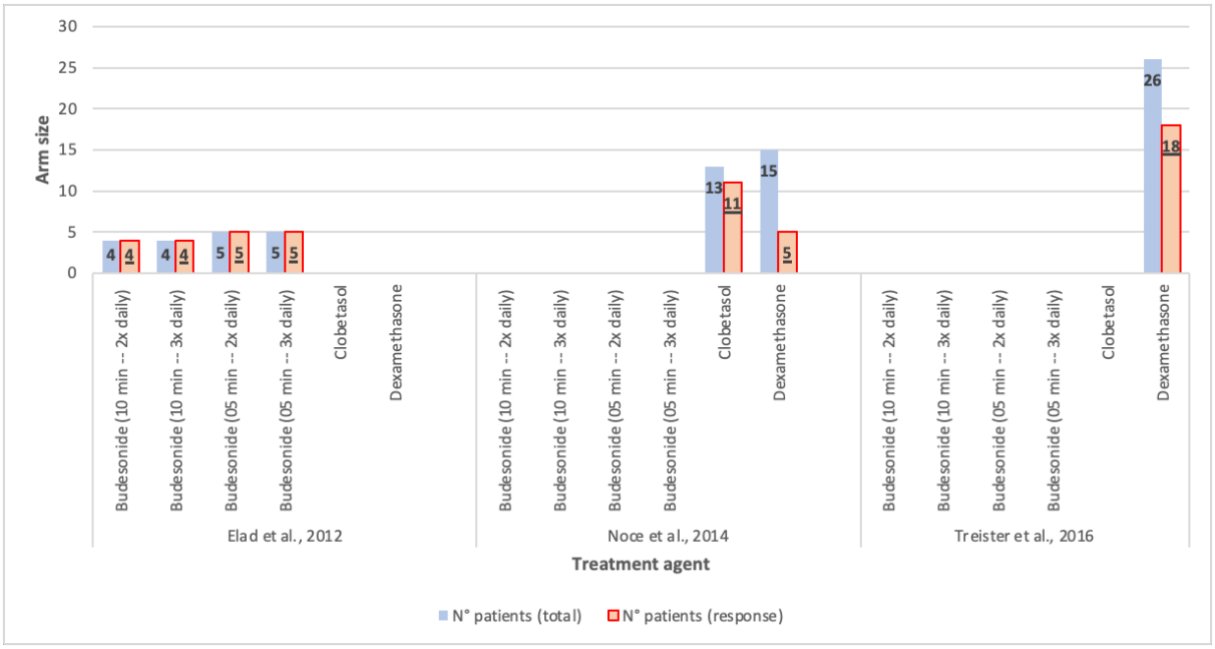

Figure 2: Comparison of overall responses.

	Section A	Section B	Section C	Section D	Overall risk
Elad *et al.* (23), **2012**	+	-	+	+	!
Noce *et al.* (21), **2014**	+	+	+	+	+
Treister *et al.* (24), **2016**	+	-	+	+	!
Mansourian *et al.* (25) **2017**	+	+	+	+	+
Bardellini *et al.* (22) **2019**	+	+	+	+	+

+	**Low risk of bias**
-	**High risk of bias**
!	**Certain risk of bias**

Figure 3: Risk of bias evaluation and legend.