Biologic Agents and Oral Diseases – An Update on Clinical Applications

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SUMMARY Biologic agents are targeted immune modulating agents that have been widely used in the treatment of inflammatory and neoplastic conditions with favorable results. The purpose of this review is to provide an update on the biologic agents that have been used in the treatment of diseases that affect the oral mucosa. Identification of relevant data, case reports and case series was performed using the PubMed-MEDLINE database and electronic databases of accredited organizations such as the European Medical Agency, US Food and Drug Administration, and clinicaltrials.gov (USA). According to the literature, the use of biologic agents in patients with oral diseases is limited mainly to patients suffering from refractory forms of immune-mediated diseases of the oral cavity. Biologic agents were used in all cases as off-label indications. Patient’s response varied, but in general biologic agents could be considered as a therapeutic option in patients with no other alternative. A point requiring extra precaution is their safety profile because severe life threatening infections are among their side effects. Another aspect that limits their broader use is their high economic cost. We aimed to provide a practical update for the clinicians who deal with oral diseases, covering as many aspects as possible of the applications of biologic agents in oral diseases reported to date.

KEY WORDS: oral diseases, biologic agents, therapy

INTRODUCTION

Biologic agents (BAs) are a relatively new category of drugs designed with the philosophy to block specific pathways involved in the pathophysiology of immune mediated and neoplastic diseases. These agents are promising a more targeted anti-inflammatory or immunosuppressive action in comparison to corticosteroids and classic corticosteroid-sparing immunosuppressants; also, they presumably represent a pathogenesis-based treatment and not just organ-based palliative therapy. The different names by which they are also referred in the literature are targeted immune modulators and biological response modifiers (1). A BAs can either be a cytokine, an antibody, or a fusion protein (1). The BAs are used in vari-
ous dermal diseases and dermatologists are familiar with their use. In this article, we aim to review the use of BAs in the diseases of the oral cavity. By reviewing the literature, we identified that the BAs adalimumab, etanercept, infliximab, alefacept, efalizumab, rituximab, epratuzumab and basiliximab have been used in diseases of the oral cavity and we present the experience from their application acquired to date.

**METHODS**

We performed literature review using PubMed-MEDLINE database and electronic data bases of accredited organizations such as the European Medical Agency (EMEA), US Food and Drug Administration (FDA), and clinicaltrials.gov (USA), by both electronic search (with the key words infliximab, etanercept, adalimumab, rituximab, efalizumab, epratuzumab, basiliximab, and alefacept, oral diseases, oral manifestations, dermatologic diseases, immune mediated diseases, biologic agents, anti-TNF agents, monoclonal antibodies, anti-B cell agents, anti T-cell agents) and hand search to identify articles that were most relevant.

**Use of biologic agents in oral diseases**

The basic characteristics of BAs applied in oral diseases are presented in Tables 1-4. Then follows presentation of oral cavity diseases in which BAs have been applied and their results.

**Oral lichen planus**

Oral lichen planus (OLP) is a chronic inflammatory condition of unknown etiology (2,3). OLP lesions may vary from asymptomatic reticular lesions to severe erosions and ulcers that are usually difficult to treat (4). Treatments for severe erosive OLP include corticosteroids (topical and systemic), azathioprine, cyclosporine, and tacrolimus. The majority of these agents usually resolve the lesions but none of them so far has been proved effective in achieving long-term remission (5). Biologic agents were used in a limited number of cases of severe recalcitrant OLP unresponsive to other treatments. Satisfactory results have been reported in a limited number of 10 patients with severe OLP that were treated with the anti-T-cell agents alefacept and efalizumab (6,7). The dosage was for efalizumab 0.7 mg/kg-1 mg/kg/week for 3-10 weeks and for alefacept 15 mg/week IM for 12 weeks (6,7). Noteworthy, one patient under efalizumab treatment developed subacute cutaneous lupus erythematosus, which led to withdrawal (8). The efficacy of these agents could be possibly attributed to their mechanism of action; efalizumab interacts with the leukocyte-function antigen-1 (LFA-1), whereas alefacept interacts with LFA-3 (9). These antigens are detectable in the majority of cells that infiltrate skin lesions of patients with lichen planus (10). In addition, these agents interact with T-cell activation, which is also important in the pathogenesis of OLP (11). A single-center, open-label, prospective pilot study of subcutaneous efalizumab for erosive OLP provides data supportive of efalizumab being beneficial for the treatment of cutaneous lichen planus (LP) and erosive OLP (8). Efalizumab is withdrawn since 2009 due to the progressive multifocal leukoencephalopathy (PML) risk, hence no other data exist (10). Also, two patients with extensive oral and cutaneous lesions were identified to be successfully treated with the anti-TNF agents etanercept (25 mg/twice weekly) and adalimumab (40mg every other week) (12,13). The success of these agents is not surprising, as TNF has been proposed to be one of the major cytokines involved in the pathogenesis of OLP (14). There is though some skepticism concerning their use, as anti-TNF agents have been reported to be the cause of lichenoid reactions with proposed mechanism of the deregulation in the balance between TNF and interferon-alpha (INF-α) (15). Furthermore, a clinical trial evaluating the possible efficacy of etanercept in the treatment of OLP has been completed and results are expected to be published (16). Also, in a single case study of severe erosive OLP, the use of the anti IL-2 receptor agent basiliximab (bolus intravenous infusion of 20 mg, 2 doses, 4 days apart) resulted in remission of oral lesions, which was only temporal as lesions reappeared soon after the agent was withdrawn (17). This agent has also been successfully used in graft versus host disease, an entity that shares histologic features with OLP (18). Basiliximab interferes with T-cell regulation; this cell has central a role during OLP pathogenesis, thus this agent could be considered as a prospective therapeutic option for severe OLP, but the cost and infection risk of basiliximab probably would form a barrier to planning appropriate clinical studies (17).

As it is evident, there is limited experience concerning the use of BAs in OLP. This is probably due to the fact that although OLP is a very painful oral condition, it does not cause debilitating morbidity or threatens life. Hence, less expensive drugs more familiar to everyday use are preferred. It would be interesting though to further investigate the possibility of BAs to reduce the recurrences in patients with severe erosive OLP (19).

**Oral pemphigus vulgaris**

Oral pemphigus vulgaris (OPV) is a chronic autoimmune bullous disease characterized by acantholysis,
Table 1. Official indications for biologic agents

<table>
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<th>Agent</th>
<th>Indications</th>
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| Infliximab | Rheumatoid arthritis  
 |                      | Crohn's disease – children 6 years and older and adults  
 |                      | Ankylosing spondylitis  
 |                      | Psoriatic arthritis  
 |                      | Plaque psoriasis – adult patients  
 |                      | Ulcerative colitis – children 6 years and older and adults                                      |
| Adalimumab | Rheumatoid arthritis  
 |                      | Juvenile idiopathic arthritis  
 |                      | Psoriatic arthritis  
 |                      | Ankylosing spondylitis  
 |                      | Crohn's disease  
 |                      | Plaque psoriasis                                                      |
| Etanercept | Rheumatoid arthritis  
 |                      | Psoriatic arthritis  
 |                      | Ankylosing spondylitis  
 |                      | Moderate to severe plaque psoriasis  
 |                      | Severely active polyarticular juvenile idiopathic arthritis in children aged 2 years and older |
| Rituximab | Non-Hodgkin's lymphoma  
 |                      | Chronic lymphocytic leukemia  
 |                      | Rheumatoid arthritis  
 |                      | Granulomatosis with polyangiitis  
 |                      | Microscopic polyangiitis                                               |
| Epratuzumab | On trial                                                                                          |
| Alefacept | Psoriasis                                                                                         |
| Efalizumab | Psoriasis  
 |                      | No longer marketed                                                        |
| Basiliximab | Prevention of acute organ rejection in the immediate post-transplant period (induction therapy) |

Source: European Medical Agency and USA Food and Drug Administration

intraepithelial blistering, and tissue and circulating antibodies against the desmosome proteins desmoglein 1 and 3 (20). Oral mucosa is the first site affected in 75% of cases and oral lesions often are more persistent than dermal lesions (21). First line therapy for PV is high dose systemic steroids (22). Prior to the use of steroids, PV had almost always fatal outcome due to extensive skin and oral ulcerations that resulted in severe infections and electrolyte disturbances (23). Today, the disease mortality is less than 10% and the main cause of mortality and morbidity is the result of chronic use of steroids and immunosuppressants, which are usually added to the corticosteroid regimen to reduce the required dose of steroids and the related side effects (24). The biologic agent rituximab has been a promising possible add-on treatment option for cases of severe PV (25,26). Rituximab was initially found to be successful treatment in patients with paraneoplastic pemphigus secondary to NHL, who were administered rituximab for the treatment of lymphoma (27,28). Since then, a certain number of one arm clinical trials that used rituximab in patients with PV unresponsive to high dose of steroids (including patients with oral mucosa involvement) appeared in the literature with promising results, but all authors underline the risk of serious infections (20,22-29). In the majority of studies, the patients received rituximab in the same dosage scheme as administered in lymphomas, in combination with low doses of prednisolone, but also in combination with other immunosuppressants and intravenous immunoglobulin G. Currently, one randomized clinical trial that compares rituximab to conventional therapy with corticosteroids is recruiting participants (30). It is unclear how rituximab exerts its positive effect on pemphigus but it is believed to eliminate the
<table>
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<th>Table 2. Major features and cost of biologic agents</th>
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<tr>
<td><strong>Agent</strong></td>
</tr>
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| Infliximab | Murine human monoclonal antibody against the soluble and the transmembrane TNF | Administration adjusted according to each indication  
Range 1.5-10 mg/kg  
Standard dose 3-5mg/kg IV every 2-6 weeks  
Clinical response after 12 weeks  
419£/100 mg vial |
| Adalimumab | Fully human recombinant IgG1 monoclonal antibody blocking both the soluble and the transmembrane TNF by creating a stable complex | 40 mg/every other week  
357.50 £/40 mg prefilled syringe |
| Etanercept | Fusion protein resembling TNF receptors type-II blocks circulating TNF and lymphoxtin-a | 25-50 mg 1-2 times/week  
178£/50 mg vial |
| Rituximab | Monoclonal antibody designed to target the CD 20 protein, expressed on the surface of B-lymphocytes | Rituximab: 375 mg per square of height in meters/week  
873.15£/50 mL |
| Epratuzumab | CD 22 humanized monoclonal antibody | 300 mg/m² every 2nd week |
| Alefacept | A fusion protein containing IgG and LFA-3, LFA-3 binds to CD-2 molecule on T-cell | 7.5 mg IV bolus  
15 mg IM once weekly  
1249$/15 mg vial |
| Efalizumab | A recombinant monoclonal antibody with high affinity to the CD-11a domain of LFA-1 | 0.7 mg/kg – 1 mg/kg  
subcutaneous injections  
1 per week  
169.20£/125 mg vial |
| Basiliximab | A chimeric murine human monoclonal antibody targeting α-chain of the T-lymphocytes interleukin-2 (IL-2) receptor | Bolus intravenous infusion of 20 mg, 2 doses, 4 days apart  
20 mg vial/842.38£ |

Source: European Medical Agency and USA Food and Drug Administration

B-cell precursors of short-lived plasma cell resulting in reduction of plasma cells secreting auto-antibodies against the main targets desmoglein 1 and 3 (31,32). Also, this agent may decrease desmoglein-specific T-cells (33,34). Due to the high risk of infections and infusion reactions and the significant cost of rituximab, it should be reserved for the very resistant PV cases or for the patients with strict contraindications for steroid use (32).

In short case report papers, the use of infliximab and etanercept in oral and cutaneous pemphigus has also demonstrated beneficial results with dramatic decrease of oral manifestations and achievement of corticosteroid tapering (35-37). A randomized controlled trial (RCT) is currently being performed by the US National Institute of Allergy and Infectious Diseases to evaluate the efficacy and safety of infliximab in patients with pemphigus vulgaris (38).

From the BAs experience in OPV, rituximab is the most feasible alternative treatment for patients with very severe pemphigus in which oral and dermal lesions persist (19). The use should always be under strict detection for the possible severe side effects (39). From the so far data, it cannot be clearly concluded that severe oral mucosal involvement without dermal or other mucosal involvement is an indication for administration of rituximab in patients with pemphigus.

Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) is part of the subepithelial vesiculobullous conditions, characterized clinically by the development of blisters and erosions and immunologically by the production of autoantibodies against proteins of the hemidesmosomes (40). Oral lesions presenting as extensive
erosions secondary to bullae eruption are a constant finding in MMP and may cause pain and dysphagia (40). Other manifestations, associated with high morbidity, are severe ocular lesions that could threaten vision and esophageal stenosis due to mucosal scarring (41). The treatment of MMP is challenging, with steroids and immunosuppressants being the first-line treatment but not always with favorable results (42). Of note, as MMP is a disease that affects the elderly population, comorbidities may constitute contraindications to their use. Case series-studies of MMP patients that have been managed with BAs also exist. In a recent 2011 study by Kasperkiewicz et al., rituximab was administered in five patients with MMP, three of whom experienced complete remission and two partial remission (43). Also, in 2010 Lourari et al. reported two MMP patients treated with rituximab; one had partial and the other complete remission after one cycle of rituximab (44). In a recent study of 25 patients with very severe MMP that received rituximab (1 or 2 cycles depending on response), 72% of patients had complete or partial response after 1 cycle (43). Of note, the authors report two deaths associated with hypogammaglobulinemia; according to patient history, these deaths could not be entirely attributed to rituximab as they had also been treated with other immunosuppressive agents (45). There are no RCTs evaluating rituximab for MMP; a single arm clinical trial with three patients on rituximab for ocular pemphigoid was conducted by the NIH and has been completed showing no ocular scarring development in all three participants (46).

The anti-TNF agents infliximab and etanercept have been reported to improve the condition of four MMP patients (one on infliximab and three on etanercept) that had persistent oral lesions unresponsive to multiple immunosuppressive treatments (45,46). The authors used standard regimens of the agents as used in psoriasis and did not refer to any significant side effects (47,48).

These findings suggest that BAs could be considered a “third-line” therapeutic option in severe cases of MMP when steroids and traditional systemic immunosuppressive drugs have failed. As MMP is an autoimmune condition in which auto-antibodies

### Table 3. Side effects of biologic agents

<table>
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<tr>
<th>Agent</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>Infusion reaction and hypersensitivity infections (viral infections, tuberculosis (TB), lower respiratory tract infection)</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B reactivation, serum sickness like reaction headache, vertigo dizziness, nausea abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Elevated transaminases, urticaria, rash, hyperhidrosis, dry skin, risk of lymphoma and other malignancies</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Lower respiratory tract infections, viral infections, upper respiratory tract infections, dizziness, headache, neurologic sensation disorders, cough, nasopharyngeal pain, diarrhea, abdominal pain, stomatitis, mouth ulcerations, hepatic enzymes increased, rash, pruritus, musculoskeletal pain, injection site reaction, pyrexia, fatigue, TB reactivation, risk of lymphoma and other malignancies</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Infections, reactions at injection site, serious infections, allergic reactions, heart failure, systemic lupus erythematosus (SLE) or lupus like syndrome, TB reactivation, risk of lymphoma and other malignancies</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Infections, HACAs (human anti-chimeric antibodies) in 9.2% in RA, leukopenia, neutropenia, infusion related reactions, angioedema, nausea, cardiac reactions, dyspnea, bronchospasm, gastrointestinal effects, decreased IgG levels (Progressive multifocal leukoencephalopathy (PML) due to JC virus has been reported with rituximab use)</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>Acute infusion reaction, headache, paresthesia</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Lymphopenia, malignancies, severe infections, hypersensitivity reactions</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Leukocytosis and lymphocytosis, flu-like symptoms, hypersensitivity, psoriasis, arthralgia, arthritis, psoriatic arthritis, back pain, elevated alkaline phosphatase and ALT, thrombocytopenia, injection site reactions, severe infections</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Gastrointestinal reactions, infections, gingival hyperplasia, hypersensitivity reactions, hemorrhage, purpura, thrombocytopenia, polycythemia, headache, tremor and dizziness</td>
</tr>
</tbody>
</table>

Source: European Medical Agency and USA Food and Drug Administration
targeting base-membrane auto-antigens have been identified, it makes sense that an anti-B cell agent such as rituximab could be an effective treatment, possibly by reducing the population of autoantibody producing B-cells (49).

Also, in the formation of subepithelial blistering, the role of multiple cytokines has been proposed, including TNF, which could partially explain the rationale of using anti-TNF agents in MMP (50). Of course, more research at the clinical and molecular level is needed to support further the use of these BAs in MMP (19).

Adamantiades-Behcet’s disease oral ulceration and recurrent aphthous stomatitis

Aphthous ulcers are a common and indolent condition, but in some cases the episodes may be so often and the duration of the ulcers so long that significantly affect the patient’s quality of life (51). Adamantiades-Behcet’s disease is classified as an autoinflammatory vasculitis (unconfined to specific vessel size or type) with main clinical characteristics of oral aphthous-like ulcers, genital ulcers, ocular and dermal lesions (52). Adamantiades-Behcet’s disease is potentially life threatening due to major blood vessels and central nervous system involvement (53). Several studies have clearly showed the positive effect of the use of infliximab and etanercept in the treatment of persistent recurrent aphthous stomatitis and Adamantiades-Behcet’s disease (54-59).

As far as recurrent aphthous stomatitis is concerned, the use of anti-TNF BAs may be an effective, but very expensive therapeutic option (19). Of interest, their successful use supports the experimental findings that TNF is the major cytokine involved in the pathogenesis of aphthae (60,61). In Adamantiades-Behcet’s disease, anti-TNF-α inhibitors proved beneficial for the improvement of ophthalmic, neurologic and joint manifestations (62,63). Hence, they are regarded as a reasonable alternative solution (64).

### Table 4. Biologic agents screening and monitoring

<table>
<thead>
<tr>
<th>Agent</th>
<th>Screening and monitoring</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>Pretreatment PPD screening, LFTs, ANA and anti-DNA, HBV, HCV, HIV, FBC regularly</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Pretreatment PPD screening, FBC, LFTs, ANA and anti-ds DNA regularly</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Pretreatment PPD screening, LFT, FBC, ANA, anti-ds DNA, HBV, HCV, HIV HIV regularly</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Pretreatment PPD screening, Blood platelets, WBC, Hemoglobin and hematocrit, LFTs, CRP, Other</td>
</tr>
<tr>
<td>Alefacept</td>
<td>CD4+ T-lymphocyte count every 2 weeks</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>FBC, LFTs, urea, creatinine regularly</td>
</tr>
<tr>
<td>Rituximab</td>
<td>FBC with differential and platelets, peripheral CD20+ cells, HBV screening, Signs or symptoms of progressive multifocal leukoencephalopathy (focal neurologic deficits, hemiparesis, visual field deficits, cognitive impairment, aphasia, ataxia, and/or cranial nerve deficits), Cardiac monitoring</td>
</tr>
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</table>

Source: European Medical Agency and USA Food and Drug Administration ANA = antinuclear antibodies; LFTs = liver function tests; FBC = full blood count; WBC = white blood count; HBV = hepatitis B virus; HCV = hepatitis C virus; PPD = purified protein derivative.
Orofacial granulomatosis

Orofacial granulomatosis (OFG) is a rare inflammatory chronic head and neck disease with main clinical features of lip swelling, oral ulcers and lymphadenopathy (65). OFG lesions microscopically show granulomatous inflammation similar to Crohn’s disease and in certain patients OFG represents extraintestinal manifestation of OFG (66). Anti-TNF antibodies have been labeled for the treatment of Crohn’s disease (65). So, as it shares common pathogenetic and histologic characteristics with OFG, one would expect that they would also be beneficial for OFG (65). In fact, the first patient with OFG treated with infliximab was reported in 2001, then another two patients that were treated with infliximab were also reported to have a very good response to therapy, but on the other hand, a patient that was treated with adalimumab developed severe facial edema and the agent was stopped despite the improvement of oral manifestations; the patients received standard doses of the agents as recommended (67-69). Elliot et al. conducted a case series study that included 14 patients with OFG who received induction to treatment with infliximab and adalimumab; the former provided good short-term response for most OFG patients although long term response was not always maintained (70). The results from the above mentioned studies are encouraging and could support the use of anti-TNF agents in OFG patients as an off-label indication when other treatments have failed, always with caution due to considerable side effects (71).

Sjögren’s syndrome

Sjögren syndrome (SS) is a common immune-related disease (primary or secondary when it coexists with other rheumatoid or other autoimmune diseases) affecting salivary and other excretory glands, joints and other organs. Salivary gland involvement results in hyposalivation experienced by the patients as xerostomia (72). Several treatment modalities have been used in primary SS patients with unsatisfactory results, including the TNF inhibitors infliximab and etanercept that were considered ineffective, as demonstrated by well conducted RCTs (73,74). As a consequence, questions have been raised regarding the involvement of TNF in the pathogenesis of primary SS (75). Infiltration of salivary gland by B-cells is important in the pathogenesis of SS and furthermore clonal populations of these cells are possibly the cause of salivary gland lymphomas that develop in SS, so anti B-cell agents such as rituximab and epratuzumab could be effective in SS (76). Rituximab as a treatment for primary SS and lymphomas associated with SS has shown promising results but additional studies are needed to support its efficacy and safety as well as the potential benefit in treating and possibly preventing SS associated salivary gland lymphomas (77-79). Epratuzumab, a humanized anti-CD 22 antibody, has shown promising results as a therapy for primary SS, according to the results of an open label phase 1-2 clinical study, in which 53% of the patients on epratuzumab reported 20%-50% symptom improvement in 6-32 weeks of treatment (80).

Targeting B-lymphocytes appears a promising treatment for severe cases of primary SS (81). The increasing evidence acquired from new studies will help determine the benefit-harm ratio from the B-cell targeting treatments.

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is an autoimmune mucocutaneous disease characterized histologically by the formation of subepidermal bullae (82). On clinical examination, patients present with skin and mucosal blisters that are more prominent on areas prone to tension and trauma (83). The pathogenetic mechanism involves the production of autoantibodies (IgG mainly but also IgA) targeting epitopes of collagen VII, the main protein of the anchoring filaments between the basic membrane and the dermis (84). Mucosal involvement may lead to oral and esophageal scarring with consequent dysphasia, while another frequent finding is severe periodontitis (85,86). Treatment modalities for EBA are not established but steroids and immunosuppressants are usually applied (87). The role of both T-cells and B-cells has been proposed in EBA pathogenesis, hence the favorable results of rituximab use in some rare cases of patients with very severe EBA unresponsive to previous therapies; the patients’ oral lesions and symptoms improved (88-90). As EBA is a rare disease, standardization of treatment protocols requires special design. The evidence concerning the success of rituximab in a limited number of patients is positive for patients with severe EBA.

CONCLUSION

In recent years, BAs have been used to treat patients with oral diseases in which an immune mediated pathogenetic mechanism is involved. As the majority of the references are case reports or case series, they are not eligible for extracting sufficient conclusions concerning the efficacy of BAs in oral diseases. The only exception is the use of rituximab in severe cases of mucocutaneous pemphigus vulgaris, for which accumulating evidence supports a significant benefit. None of the reviewed diseases has an official
indication for any type of BA. The decision to use a BA in all the reported cases was based on the pathogenesis of diseases, which justified the rationale of its use. Also, the authors exploited previous experience in diseases with clinical and pathogenetic similarities. Furthermore, the therapeutic protocols used were “borrowed” from the BAs official indications. So far, these targeted immunomodulating agents can only constitute a potential therapeutic option in refractory cases of oral diseases unresponsive to usual treatments. As these agents have considerable side effects, especially infections that in some cases resulted in death, extended studies with homogeneous protocols are required to establish their efficacy and safety. Finally, the cost of these agents is very high and should be considered prior to their clinical use. Many of the patients with severe recalcitrant mucocutaneous diseases are likely to seek help of dermatologists, especially in tertiary hospital units; hence this comprehensive update summarizing the accumulated experience from BAs in oral diseases could assist in clinical decision making.

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