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1 **Title**

2 WWOM VII: A systematic review of immunobiologic therapy for oral manifestations of pemphigoid and
3 pemphigus

4 **Running title**

5 WWOM VII: Biologics in pemphigoid and pemphigus

6
7 **Keywords:**

8 mucous membrane pemphigoid, pemphigus vulgaris, blistering disease, biologic agents, rituximab,
9 autoimmunity

10
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40

41 **Abstract**

42 **Objective.** To assess the evidence for treatment of oral involvement of pemphigus and pemphigoid with
43 biologics.

44 **Study Design.** This systematic review used a comprehensive search strategy to identify literature
45 describing oral involvement of pemphigus or pemphigoid treated with a biologic agent. The primary
46 outcome measures were efficacy and safety of biologic therapy.

47 **Results.** Inclusion criteria was met by 154 studies including over 1200 patients. Treatment of pemphigus
48 with a total of 11 unique biologic agents and 3 unique combinations of agents is reported. Five randomized
49 controlled trials (RCT) were included in the final analysis that investigated infliximab, IVIg, rituximab and
50 autologous platelet-rich plasma therapy for pemphigus vulgaris. Three non-RCT studies reported on
51 successful rituximab or IVIg therapy for mucous membrane pemphigoid. Studies demonstrated
52 considerable heterogeneity in agent, methods, and quality.

53 **Conclusions.** Evidence clearly describing oral tissue response to biologic therapy is sparse. Two RCTs
54 support use of rituximab, one supports use of IVIg, and one pilot study suggests intralesional injection of
55 autologous platelet-rich plasma aids healing of oral PV lesions. As oral lesions of pemphigus and
56 pemphigoid can be refractory to systemic therapy, drug trials including biologic therapies should
57 document details regarding response of the oral lesions to therapy.

58

59

60 **Introduction**

61 Biologics have gained recognition as promising therapies for inflammatory and autoimmune
62 disorders, and there is significant interest in evaluating the potential of this drug class for the treatment
63 of complex oral disease. A biologic or biologic therapy is defined as a substance that is made from a living
64 organism or its products to treat disease (NCI Cancer Dictionary). Strides have been made in the treatment
65 of the autoimmune epidermal blistering disease pemphigus using biologics, and the United States Food
66 and Drug Administration (FDA) approved the use of a biologic agent, rituximab, for the treatment of adults
67 with moderate to severe pemphigus vulgaris (PV) in June 2018.

68 Pemphigus consists of a group of autoimmune diseases characterized by epithelial blistering affecting
69 cutaneous and/or mucosal surfaces. Intraepithelial blister formation results from the loss of adhesion of
70 keratinocytes (acantholysis), with immunoglobulin G (IgG) antibodies directed against desmosomal
71 proteins. PV is the most common and most aggressive variant (Baum et al., 2016). The oral mucosa is the
72 site of initial presentation in 50-75% of cases (Mustafa, Porter, Smoller, & Sitaru, 2015; Robinson, Lozada-
73 Nur, & Frieden, 1997; Shamim, Varghese, Shameena, & Sudha, 2007).

74 The complex pathogenesis of PV involves the generation of autoantibodies against connective
75 proteins of the skin and mucosa including desmosomal cadherins (Saito et al., 2012). Desmoglein 3 is the
76 major antigen, but 50–60% of patients also have anti-desmoglein 1 antibodies (Cozzani et al., 2013;
77 Kasperkiewicz et al., 2017). The clear role of autoantibodies in PV pathogenesis suggests an important
78 therapeutic role for targeted agents that block the generation or survival of autoreactive immune
79 components (Ellebrecht & Payne, 2017).

80 The mainstay of treatment of pemphigus is immunosuppressive therapy (Ahmed, 2001, 2007).
81 Management consists of two main phases: induction of remission and maintenance of remission. For
82 decades, systemic corticosteroids have been the therapy of choice for induction with maintenance

83 effected by azathioprine, mycophenolate mofetil, dapsone, methotrexate, cyclophosphamide, gold, and
84 cyclosporine. Adjuvant techniques to reduce antibody load include plasmapheresis, and
85 immunoadsorption (McMillan et al., 2015). Mucocutaneous PV tends to be a more severe disease, with
86 oral lesions being slower to respond to treatment and less likely to achieve remission off-treatment than
87 solely cutaneous disease(Kavusi et al., 2008). There have been recent international attempts to
88 standardize the diagnosis and management of pemphigus, and newer therapies such as biologics or
89 intravenous immunoglobulin (IVIg) therapy may offer significant advantages over systemic corticosteroids
90 (Ellebrecht & Payne, 2017; Hertl et al., 2015; D. F. Murrell et al., 2018).

91 Mucous membrane pemphigoid (MMP) is a rare, predominantly mucosal subepithelial blistering
92 disorder involving the oral mucosa, conjunctiva, anogenital tissues, and upper aerodigestive tract. Wide
93 variation in disease severity ranges from minimal painless oral involvement to severe blistering with
94 scarring sequelae. Several basement membrane proteins are associated with autoantibody reactivity
95 including BP180, BP230, both subunits of $\alpha 6\beta 4$ integrin, laminin 332, and type VII collagen(Enno Schmidt
96 & Zillikens, 2013). Mild disease is managed with topical steroids and moderate/severe disease with short-
97 term prednisone and long-term mycophenolate mofetil, azathioprine or dapsone (Taylor et al., 2015).

98

99 Based upon the rationale that pemphigus and mucous membrane pemphigoid are primarily
100 autoantibody-driven autoimmune disorders, therapies that deplete autoreactive B cells have been
101 investigated for the treatment of these disorders (Nagel, Hertl, & Eming, 2009). Rituximab is a chimeric
102 murine–human monoclonal antibody of the IgG1 subclass, directed against the B-lymphocyte-specific
103 antigen CD20, expressed by early B cells in the bone marrow, autoantigen-specific B cells, memory B cells
104 and mature B cells (Nagel et al., 2009). Rituximab was first used to treat PV in the early 2000s in patients
105 refractory to conventional treatment. By 2007, several case series had emerged showing efficacy (Ahmed,

106 Spiegelman, Cavacini, & Posner, 2006; Joly et al., 2007; E. Schmidt, Seitz, Benoit, Brocker, & Goebeler,
107 2007). Following treatment with rituximab there is rapid and sustained (6–12 months) depletion of
108 circulating and tissue-based B cells. Initial studies for dosing for rituximab in immunobullous disorders
109 reflected a regimen derived from the treatment of patients with lymphoma, using four weekly infusions
110 of 375mg/m² (Joly et al., 2007). Since then, clinicians have adopted an alternate regimen: two infusions
111 of 1000mg separated by two weeks (Y. A. Leshem et al., 2014; Yael A. Leshem, Hodak, David, Anhalt, &
112 Mimouni, 2013). Advantages of this regimen include fewer infusions and a lower total dose of rituximab.
113 Less data is available for rituximab use in MMP.

114 The Seventh World Workshop in Oral Medicine sponsored this systematic review to evaluate the
115 efficacy of biologic therapies in the management of pemphigus, including subtypes PV and Paraneoplastic
116 pemphigus (PNP), and MMP involving the oral mucosa, with or without cutaneous lesions. The study
117 summarizes the evidence supporting the use of biologics as first line, second line or adjuvant therapy in
118 these conditions. This review also highlights the wide variation in clinical practice and the need for high-
119 quality research to validate current guidelines and to explore future therapies.

120

121 **Methods**

122 A systematic review was conducted following a detailed protocol. Key aspects of the protocol are
123 summarised here.

124 **Inclusion Criteria**

125 Randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies (e.g., cohort
126 studies, case series and case reports) were included. Studies investigating biologic treatments for PV, PNP
127 and MMP with oral involvement were included. Case reports, case series, meeting abstracts and clinical

128 observations were included only if there was a clear description of biologic therapy for patients with oral
129 disease.

130 Data from study participants were included if accepted criteria in all three diagnostic domains: clinical
131 presentation, histology, and immunofluorescence was met and there was evidence of oral mucosal
132 involvement and assessment.

133 **Exclusion criteria**

134 Studies describing only cutaneous disease, those that reported primarily on cancer therapy, papers with
135 insufficient information about oral manifestations of disease or oral tissue response to therapy, non-
136 English papers, and full text unavailable papers were excluded. For duplicate reports or datasets
137 identified, only the most final version of the paper was included. Some studies included in the final
138 dataset included a mixed disease cohort. Participants with cutaneous disease only or involvement at only
139 non-oral sites were excluded from data extraction when individual patient response data were available.

140 **Types of interventions**

141 Active biologic treatment included any preventive, palliative, or curative intervention administered
142 systemically aimed at the treatment of PV, PNP and MMP meeting the United States National Institutes
143 of Health, National Cancer Institute definition of a biologic or biologic therapy: a substance that is made
144 from a living organism or its products to treat disease.

145 **Types of outcome measures**

146 Primary outcome measures were efficacy and safety. Secondary outcome measures included time to
147 disease control, time to disease relapse, disease severity score, serum antibody titers, and quality of life.

148 **Electronic searches**

149 Assisted by a research librarian (RP), MEDLINE® (via PubMed), Embase, Scopus and the Cochrane Library
150 from date of database inception through October 26, 2018 were searched using general terms for

151 biologics, or terms for specific drugs or drug classes combined with terms for pemphigus, pemphigoid, or
152 other related diseases. Either medical subject headings (MeSH) or Embase subject headings (Emtree)
153 where available and keywords when applicable were used. Conference papers were searched in Embase
154 and Scopus. The electronic search excluded all non-English language papers which did not have an English
155 version. This study was structured according to PRISMA statement for reporting of systematic review and
156 meta-analysis.

157 **Searching other resources**

158 We reviewed the bibliographies of RCTs and review articles and searched clinical trial databases
159 (ClinicalTrials.gov (ClinicalTrials.gov) and World Health Organization (WHO) International Clinical Trials
160 Registry Platform (ICTRP) (apps.who.int/trialsearch/)) to identify additional published or unpublished
161 data. We did not contact investigators or study sponsors. The detailed search strategy is provided in the
162 online Supplementary Material Appendix 1.

163 **Selection of studies**

164 Abstracts of each search-identified study were evaluated by two authors who reached agreement for
165 inclusion. Studies that clearly did not satisfy the inclusion criteria were eliminated, and full copies of the
166 remaining studies were obtained. Two review authors (BPC, JWM) read the studies independently and
167 reached agreement by discussion. Studies were not anonymized before assessment. Study tracking
168 through the selection process was completed using Covidence systematic review software ("Covidence
169 systematic review software,"). The flow of studies is illustrated in a PRISMA flow chart (Liberati et al.,
170 2009).

171 **Data extraction and management**

172 One review author (BPC or JWM) extracted data independently, using a standard custom data extraction
173 form for full studies (online Supplementary Material Appendix 2) and a short data extraction form for case
174 reports and case series (online Supplementary Material Appendix 2) through Google Forms which
175 concatenated results into a database. Forms were based on STROBE criteria (von Elm et al., 2008). Data
176 extraction was cross-checked by the other author against the full manuscript.

177

178 **Assessment of risk of bias in included studies**

179 Two review authors (BPC, JWM) independently assessed then cross-checked and discussed the
180 assessment of risk of bias for each RCT (n=5). The revised Cochrane tool to assess risk of bias in randomized
181 trials (RoB 2) for individually-randomized, parallel-group trials (October 2018) was used to assess the RCTs
182 across five domains: 1. Bias arising from the randomization process; 2. Bias due to deviations from
183 intended interventions; 3. Bias due to missing outcome data; 4. Bias in measurement of the outcome; and
184 5. Bias in selection of the reported result (Higgins JPT). Risk of bias for each domain was assessed as “high,”
185 “low,” or “some concerns.” A study with one or more “high” risk of bias judgments for any given domain
186 was deemed overall to have a high risk of bias.

187 **Data synthesis and measures of treatment effect**

188 Case reports and series were scored to evaluate the question, “Was the therapy effective in managing the
189 oral disease?” the outcomes of each study were categorized by reviewers during data extraction on a 4-
190 point scale: Completely Effective (in all patients), Mostly Effective in more than 50% of patients (not totally
191 effective), Partially Effective (in less than 50% of patients treated with biologics--this option selected if
192 data were unclear about %, but drug was not effective in all patients), or Ineffective in all patients.
193 Effectiveness was based on the outcome criterion within the individual study. The category was assigned
194 by one reviewer and confirmed by a second, and any disparity was settled through discussion. Studies

195 that included multiple types of pemphigus or pemphigoid diagnoses were excluded from this overview
196 analysis, which limited the categorical summary to case reports and case series, as all other study types
197 had mixed disease cohorts. The results are reported as percent of total reports for that drug and disease
198 category.

199
200 **Results**

201
202 From 6416 unique records, we identified 165 studies including more than 1200 patients with oral
203 involvement of pemphigus or pemphigoid treated with a biologic agent. Due to the emerging nature of
204 this field, case reports and case series were included in this review and comprised 80% of the number of
205 total publications and 47% of the overall patients (Figure 1). The remaining 29 full studies were comprised
206 of 5 randomized controlled trials, and 24 non-randomized studies (3 non-randomized controlled trials, 14
207 cohort studies, and 7 non-controlled trials). Specific biologic agent and dosing varied across studies and
208 was variably reported. Studies included 11 unique biologic agents and 3 combination therapies. The
209 breakdown of publication type by biologic therapy is shown in Figure 1b. MMP or PNP was not the topic
210 of any identified RCTs. Most (135/154, 88%) of the included studies used biologics as salvage therapy in
211 heavily-treated patients who were refractory to other modalities.

212 Detailed analysis of the 5 RCTs for the treatment of pemphigus are summarized below and in
213 Table 1. Four studies were classified as parallel RCTs (Joly 2017, Hall 2015, Kanwar 2014, Amagai 2009)
214 and one was a 'split-mouth' RCT (El-Komy 2018). Three of the studies were multicenter (Joly 2017, Hall
215 2015, Amagai 2009). Two of the RCTs used placebo controls (Hall 2015, Amagai 2009) but allowed both
216 groups to continue some form of active pharmaceutical intervention (i.e. systemic steroids). All the RCTS
217 used clinical outcome measures, however, there was considerable heterogeneity in the specific outcome
218 measures employed. Reduced dosage of corticosteroids and PV antibody titers were used as surrogate
219 markers for treatment efficacy in several studies. Because of the heterogeneity of outcomes for each of
220 the studied interventions, quantitative meta-analysis could not be conducted. Analyses of the relevant

221 outcomes (relative risks and 95% CIs) from the RCTs are summarized in detail below. A quality assessment
222 of included randomized controlled trials was performed using Cochrane Risk of Bias (RoB 2.0) and is
223 detailed in Supplemental Figure 1.

224 Rituximab was tested in 2 RCTs that included assessment of the oral mucosa. Kanwar *et al.*
225 conducted randomized comparative observer-blinded pilot study that compared two rituximab dosing
226 regimens for the treatment pemphigus (Kanwar et al., 2014). Patients with active PV (n=15) or PF (n=7)
227 who were treatment-naive, resistant to previous therapies, or who had severe disease were recruited
228 from a dermatology department in a tertiary care setting in India. They were randomized to receive either
229 two doses of 500 or 1000 mg rituximab at an interval of 15 days and were followed for 48 weeks. The
230 primary endpoint was clinical efficacy between treatments in terms of early (time to disease control and
231 time to complete consolidation phase) and late end points [partial response (PR) and complete response,
232 (CR)] on the Ikeda severity score scale as assessed by an examiner blinded to treatment group (Ikeda et
233 al., 2003). No significant adverse events (SAEs) were recorded in either group, though AEs including mild
234 infusion reactions, upper respiratory tract infections, diarrhea, striae and acneiform eruptions were seen
235 in both groups. The mean number of AEs was 1.36 in the 2x500 mg group and 1.45 in the 2x1000 mg
236 group. At week 40, the fall in Ikeda severity score was steeper in the 2x1000 mg group than in 2x500 mg
237 group (P = 0.049). Patients in the 2x500 mg group received a significantly higher cumulative dose of
238 azathioprine (P = 0.018). ELISA indices of Dsg1 and Dsg3 showed a statistically significant decline in the
239 2x1000 mg group only, and B cell repopulation occurred earlier 8 weeks earlier in the 2x500 mg group.

240 In 2017, Joly and colleagues published results from an open-label multicenter parallel RCT
241 comparing oral prednisone alone versus rituximab and a short-term prednisone regimen to treat newly-
242 diagnosed pemphigus (Joly et al., 2017). Pemphigus patients with PV (n=74) or PF (n=16) were recruited
243 at 25 centers in France and randomized to one of 2 groups: oral prednisone alone starting at 1.0 or 1.5
244 mg/kg/day, tapered over 12-18 months (n=44) , or 1000 mg intravenous rituximab on days 0 and 14, and

245 a 500 mg dose at months 12 and 18 combined with a short-term prednisone treatment of 1.0-
246 1.5mg/kg/day tapered over 3-6 months (n=46). Stratification by severity of pemphigus was included in
247 the randomization matrix, and moderate-to-severe pemphigus was defined as skin involvement of greater
248 than 5% body surface area, or significant mucosal involvement defined as more than ten mucosal
249 erosions, or diffuse gingivitis or confluent large erosions, or involvement of two or more mucosal sites.
250 Scoring of the oral mucosa was incorporated into the mucous membrane subsection of the Pemphigus
251 Disease Area Index (PDAI) scoring tool, however, oral tissue subscores were not reported for this study
252 (Dedee F. Murrell et al., 2008). Patients assigned to rituximab plus short-term prednisone had significantly
253 fewer SAEs (mean 0.59 [SD 1.15]) than patients those assigned to prednisone alone (mean 1.20 [SD 1.25]),
254 which was attributed to the lower cumulative steroid dose in the rituximab group. At the primary
255 endpoint, month 24, 41 (89%) of 46 patients assigned to rituximab plus short-term prednisone were in
256 complete remission off-therapy versus 15 (34%) of 44 assigned to prednisone alone ($p < 0.0001$). The
257 corresponding relative risk of success of is 2.61 (95% CI 1.71–3.99, $p < 0.0001$). Data from this study
258 demonstrate a clear benefit of rituximab as a first-line therapy for pemphigus patients, including those
259 with severe oral mucosal manifestations.

260 Inflammation is a significant factor in the feed-forward circuit of autoimmune disease. Tumor
261 necrosis factor alpha (TNF- α) is cytokine that has been detected in the skin lesions of patients with PV,
262 and serum levels of TNF- α have been correlated with disease activity. In 2015, Hall *et al.* reported
263 treatment of pemphigus patients using infliximab, an inhibitor of TNF- α (Hall et al., 2015). This double-
264 blinded, placebo-controlled trial was carried out at 6 centers in the United States. Ten patients received
265 infusions of infliximab (5 mg/kg) at weeks 0, 2, 6 and 14 while receiving standard-of-care with follow-up
266 at weeks 10, 18, 22 and 26. Ten control group patients received infusions of placebo at weeks 0, 2, 6 and
267 14 while receiving prednisone with follow-up at weeks 10, 18, 22 and 26. To qualify for the study, patients
268 were required to score moderate or severe on both the mucosal and cutaneous subsections of a disease

269 activity score. For the mucosal subsection, a moderate score required 6–10 lesions/small ulcers. This scale
270 was used for clinical scoring at each study visit. In this trial, the primary endpoint was defined as response
271 to treatment at week 18. Subjects were responders if they achieved a prednisone dosage \leq 25% of the
272 initial starting dose or \leq 10 mg daily and had no new blisters within the previous 4 weeks. Groups did not
273 differ in AE incidence, and no infectious complications of Grade 3 or greater (Common Terminology
274 Criteria for Adverse Events, CTCAE 3.0) were reported (Trotti et al., 2003). At the primary endpoint, week
275 18, one subject in each group had responded. At week 26, three infliximab-treated subjects versus none
276 in the placebo group had responded. Assessment of IgG anti-Dsg1 and anti-Dsg3 antibody titers found
277 significantly lower levels in infliximab-treated patients at week 18 and 26. Study authors concluded that
278 infliximab therapy was not shown to be clinically effective for the treatment of patients with PV.

279 Intravenous immunoglobulin (IVIg) is used as an adjuvant steroid sparing agent in PV or as a
280 monotherapy. It is a purified product consisting mostly of IgG molecules made from a pool of donors and
281 is thought to have multiple mechanisms of action including downregulation of antibody production by
282 plasma cells (Hartung, 2008). Amagai and colleagues conducted a three-arm clinical trial to test two doses
283 of IVIg versus placebo using a new outcome measure, time to escape protocol (length of time participant
284 stayed on protocol without requiring additional treatment up to day 85, TEP) (Amagai et al., 2009).
285 Pemphigus patients, including PV (n=40) and PF (n=21), received a 200mg IVIg, 400mg IVIg, or placebo
286 infusion administered in divided doses over 5 days plus oral steroids. TEP was the primary endpoint of the
287 study. Secondary endpoints included change in pemphigus activity score (PAS) which specifically scores
288 oral mucosal and skin lesions. At day 85, AEs, called adverse drug reactions in this study, occurred in 29%
289 of the 400mg group, 35% of the 200mg group and 25% of the placebo group, with no statistical differences
290 between groups. By day 85, 11/20 patients on placebo required elevated treatment (escape), 4/20
291 patients in the 200mg IVIg group escaped after 10+ days, and 2/21 patients on 400mg IVIg escaped after
292 22+ days. A log-rank test was used to compare treatment groups to placebo only and found a significant

293 change in TEP between placebo and the 400mg group ($p < 0.001$). The PAS, which included mucosal scoring,
294 was significantly changed (decreased) from baseline at all time-points in the 400mg group, after day 15
295 only in the 200mg group, and not significantly changed in the placebo group. Similarly, anti-Dsg1 and Dsg3
296 IgG titers were decreased at day 43 and 85 in the 400mg group, at day 85 only in the 200mg group, and
297 not at all in the placebo group.

298 Direct therapy may be applied to isolated oral lesions or those refractory to systemic treatment.
299 Autologous platelet-rich plasma (PRP) has been used locally to accelerate cutaneous and oral wound
300 healing, and to treat refractory oral ulcers in autoimmune conditions (Bojanic et al., 2018; Lacci & Dardik,
301 2010). In 2018, El-Komy *et. al.* reported a pilot single center randomized double-blind study comparing
302 local injection of PRP on one side of the mouth with active standard treatment: local injection of
303 triamcinolone acetonide on the contralateral side (El-Komy, Saleh, & Saleh, 2018). The trial was conducted
304 in an Egyptian hospital in 11 PV patients with oral pain or oral lesions. Buccal mucosa or gingiva was
305 injected every 14 days for 3 months with 1 milliliter of autologous PRP at the base and side of the erosion,
306 and on the opposite side with 10 mg/ml triamcinolone. Patient and scoring physician were blinded to the
307 treatment assignment. Scoring was completed per the oral PDAI for the primary endpoint of oral lesion
308 improvement after 90 days. No AE summary was provided for the study. Nine patients completed the
309 study, and triamcinolone injection decreased the mean oral PDAI from 2.3 to 0.9, and PDAI scores after
310 PRP injection moved from 2.6 to 1.0. Statistically equivalent clinical improvement was measured when
311 refractory oral ulcers of PV were injected with either steroid or PRP.

312 MMP patients were included in 1 non-randomized controlled trial and 2 cohort studies that used
313 IVIg treatment, 2 cohort studies that examined rituximab treatment (Table 1). Sami *et. al.* reported on 7
314 severe oral pemphigoid patients treated with IVIg therapy versus 7 similar patients on standard therapy
315 (N. Sami, Bhol, & Ahmed, 2002). The primary outcome was change in the anti-human alpha6 integrin
316 antibody titers, which have a pathophysiologic role in blister formation in OP. Titers in the IVIg group

317 dropped at a similar rate to controls through month 4 of treatment, but then declined at a significantly
318 faster rate after six months of treatment ($P = 0.03$). A case series that examined patients with autoimmune
319 mucocutaneous blistering diseases on monthly courses of IVIg included 4 MMP patients (Segura et al.,
320 2007). One had a complete clinical response, 2 had a partial response and 1 did not respond to treatment.
321 Steroid refractory MMP patients ($n=15$) were treated with IVIg in a separate non-controlled study (Naveed
322 Sami, Bhol, & Razzaque Ahmed, 2002). All (15/15) patients had effective clinical response and were able
323 to discontinue previous systemic therapies, with no reported AEs. Salvage therapy with rituximab has
324 been reported in 4 patients across 2 case series that included MMP patients (Kolesnik et al., 2014; E.
325 Schmidt, Seitz, Benoit, Bröcker, & Goebeler, 2007). One patient had clinical progression of MMP (51) on
326 rituximab combined with immunoadsorption, 2 patients achieved a complete response (reduction in dose
327 of systemic immunosuppression) after several (number varied) rituximab infusions, and 1 patient had a
328 partial response.

329 Scoring of the case reports and case series in the dataset was done to answer, “was the therapy
330 effective in managing oral disease?” Results of each study were categorized as: Completely Effective (in
331 all patients), Mostly Effective in more than 50% of patients (not totally effective), Partially Effective (in
332 less than 50% of patients treated) or Ineffective in all patients. In the case studies and series using
333 rituximab in pemphigus vulgaris with oral involvement ($n=48$), rituximab was Completely Effective in
334 managing oral disease in 40% of cases and Mostly Effective in 48% of cases. It was Partially Effective or
335 Ineffective in 6% each of case reports or series. For MMP ($n=11$), rituximab was Completely Effective in
336 45% of cases, Mostly Effective in 27% of cases and Partially Effective in 27% of cases. A wider response
337 distribution is noted in cases of PNP treated with rituximab ($n=14$), in which 29% of cases were Completely
338 Effective, 21% of cases were Mostly Effective, 21% were Partially Effective, and rituximab was Ineffective
339 for PNP in 29% of cases. IVIg was reported to be Completely Effective for treatment of MMP in all case

340 reports or series (n=6). For PV (n=11), IVIg was Completely Effective in 9% of cases, Mostly Effective in
341 64% of cases, Partially Effective in 18% of cases and Ineffective in 9% of cases.

342
343 **Discussion**

344 In this systematic review, we assess the evidence base for treating oral manifestations of
345 pemphigus and pemphigoid with biologics. The literature which clearly describes response to biologic
346 therapy in the oral tissues affected by pemphigus and pemphigoid is sparse, and randomized controlled
347 studies are thus far limited to the treatment of pemphigus. Five RCTs were identified by the search
348 parameters, along with 24 other non-controlled or non-randomized studies using biologic agents to treat
349 pemphigus or pemphigoid. Two RCTs support use of rituximab to reduce total cumulative corticosteroid
350 dose and associated side effects. One trial that included heterogenous group of new-onset and refractory
351 patients found that higher doses of rituximab (two doses of 1000 mg at a 15-day interval) were more
352 effective. A second RCT treated new-onset PV patients only with a modified rituximab regimen of 1000
353 mg on days 0 and 14, and 500 mg at months 12 and 18 along with a steroid pulse, and at 24-months on
354 study, 89% of rituximab-treated patients were in full remission (off therapy) while only 34% of steroid-
355 only-treated patients were off therapy for pemphigus. Unfortunately, limited specific information was
356 available from these trials regarding oral mucosal response to rituximab therapy. The trial of IVIg included
357 patients with moderate-severe oral mucosal lesions and found that 400mg doses of IVIg were superior to
358 placebo in preventing pemphigus flares requiring escalated therapy. Finally, one small pilot study suggests
359 that intralesional injection of autologous platelet-rich plasma may aid in healing of oral PV lesions when
360 intralesional steroids are contraindicated, equivalent to triamcinolone acetonide injection, however
361 significant concerns exist with the small size and design of this study – specifically that agents given on
362 one side of the mouth may have affected lesions on the contralateral side. Results of infliximab therapy
363 for pemphigus found that it neither reduced systemic prednisone dosage required nor reduced
364 occurrence of new lesions. The four agents investigated in RCTs: rituximab, infliximab, IVIg, and PRP had

365 equivalent safety profiles to that of control agents, generally standard-of-care steroid regimens, in the
366 studies.

367 Any analysis of the case reports and case series included in this literature survey is inherently
368 biased and should be interpreted with caution, as single case studies are rarely published to report
369 treatment failures. IVIg and rituximab are the most reported agents in these papers, and those agents
370 have been tested in some form of RCT for pemphigus. They have performed well, but with lower success
371 rates than suggested by the case reports/series descriptive analysis.

372 Data from the July 2017 study was the basis for the United States FDA approval of the use of
373 rituximab for the treatment of adults with moderate to severe pemphigus vulgaris (PV) in mid-2018.
374 Additional trials are in progress and it is anticipated that treatment of PV with rituximab will soon be
375 better described in the literature.

376 New targeted therapeutic agents are in development for treatment of pemphigus that could
377 further limit side-effects through more precise targeting of autoimmune pathobiology. These include
378 chimeric antigen receptor therapy to target anti-desmoglein-3-specific B cells that produce pathogenic
379 pemphigus autoantibodies (Ellebrecht et al., 2016), blockade of T-cell co-receptors such as CD154 that are
380 required by B cells for stimulation of autoantibody production, and a Bruton's tyrosine kinase (BTK)
381 inhibitor that is in active clinical trials for PV (Principia Biopharma, 1993–2018), among other promising
382 strategies.

383 Another emerging nuance of this field that is beyond the scope of this review are the reports of
384 oral bullous lesions induced by biologic therapies (Naidoo et al., 2016; Vigarios, Epstein, & Sibaud, 2017).
385 These may occur after checkpoint inhibitor or other biologic therapy for myriad conditions and can
386 present with a standard serologic and histologic profile of pemphigus or pemphigoid. These cases are

387 typically addressed with interruption of biologic therapy and initiation of systemic and topical steroids but
388 may need differential clinical management versus non-drug-induced bullous disease.

389 Oral lesions of pemphigus and pemphigoid can be refractory to systemic therapy, and in this
390 emerging drug class, it is critical to report on the timing and response of the oral cavity to biologic therapy
391 from clinical trials to aid in the clinical decision-making process for patients with severe or primarily oral
392 manifestations of bullous disease. Evidence is missing from the literature that could guide earlier
393 recommendations for biologic therapy to address problematic oral manifestations. Given the challenges
394 of treating these conditions, it would be helpful for future RCTs and case-control studies to (1) include an
395 oral-specific scale or report on oral mucosal outcomes that are often scored as part of comprehensive
396 scales such as the PDAI and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), (2) track and report
397 timing of disease resolution at specific sites (oral vs ocular vs skin), (3) describe site-specific symptoms
398 including oral symptoms and the timing of response of these to biologic (or other) therapies, (4) include
399 patient-reported outcomes tracking better or worse control of pain and discomfort at mucosal sites and
400 tolerance of biologics versus traditional therapies.

401 **Conflicts of Interest:** ASP holds equity in Cabaletta Bio, focused on targeted therapy of autoimmune
402 diseases including pemphigus, and is an inventor on patents licensed by Novartis and Cabaletta Bio for
403 autoimmunity.

404

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Study	Year	Intervention	Country	Study Type	No of sites	No of patients	Sex, M:F	Age (yr)	Disease	Disease Status	Disease Duration (mean)	Biologic Dose	Adverse Effects
Joly et al	2017	Rituximab	France	RCT	25	90	40:50	53.3	Pemphigus vulgaris, pemphigus foliaceus	Initial	97.8 days	1000mg day 1 and 14, then 500mg at 12m and 18m	Headache, asthenia, fever, chills, nausea, septicemia, pyelonephritis, death
Hall et al	2015	Infliximab	USA	RCT	6	20	12:8	53.25	Pemphigus vulgaris	Refractory	Not stated	5mg/kg at weeks 0, 2, 6 and 14	No infectious complications
Kanwar et al	2014	Rituximab	India	RCT	1	22	11:11	33.4	Pemphigus vulgaris, pemphigus foliaceus and pemphigus erythematoid	Refractory	20.2 months	500mg or 1000mg, two doses, 2 weeks apart	Infusion reactions, upper respiratory tract infections, diarrhoea, stria, acneiform eruptions
Amagii et al	2009	IVIG	Japan	RCT	27	61	27:34	53.36	Pemphigus vulgaris, pemphigus foliaceus	Refractory	24.4 months	200mg or 400mg/kg/d, divided over 5 consecutive days	Headache, aggravated chronic hepatitis C, decreased lymphocytes, palpitations, abdominal discomfort, constipation, nausea, pain at the injection site, increased creatinine, increased blood pressure, decreased platelet count, hepatic dysfunction, common cold, muscle pain.
El-Komy et al	2018	Platelet rich plasma	Egypt	Split-mouth RCT	1	11	4:7	41.1	Pemphigus vulgaris	Refractory	4mo - 8 years	1ml intralesional PRP every 14 days for 3 months	None
Kolesnik et al	2014	Rituximab	Germany	Cohort	1	3	2:1	68.7	Mucous membrane pemphigoid	2 refractory, 1 no prior treatment	35.3 months	375 mg/m ² at weekly intervals x 4	Infection in 1 case
Schmidt et al	2007	Rituximab	Germany	Cohort	1	1	M=1	78	Mucous membrane	Refractory	64 months	375mg/m ² at weekly intervals x 4	None

pemphigoid													
Segura et al	2007	IVIG	Spain	Cohort	1	4	3 female, 1 not defined	70.8	Mucous membrane pemphigoid	Refractory	88.5 months	2 g/kg/cycle over 4 or 5 consecutive days	Cephalgia, hypertension, epistaxis, headache, fever, N+V+D
Sami et al	2002	IVIG	USA	Non-randomised trial	1	7	2;5	55.5	Mucous membrane pemphigoid	Contraindication to immunosuppressive therapy	Not stated	1-2 g/kg/cycle infused over 3 consecutive days	None
Sami et al	2002	IVIG	USA	Cohort	1	15	7;8	66	Mucous membrane pemphigoid	Refractory	Not stated	1-2 g/kg/cycle infused over 3 consecutive days	No side effects reported

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