contraindications to oral CS and of comorbidities (such as diabetes, severe osteoporosis and significant cardiovascular problems) or in patients with extensive BP (4.56 ± 0.76). Nevertheless, there is no positive evidence supporting their use as a first-line treatment and they are therefore non-validated.[44–46] The use of immunosuppressive drugs may be recommended either in the large group of patients with relapsing BP or in the few patients having recalcitrant BP who are not adequately controlled by topical or oral CS (4.78 ± 0.77).

In brief, the following molecules may be recommended (see Table 3):

- *Azathioprine*: 1 to 3 mg/kg/day according to TPMT activity[54–56];
- *Mycophenolates* (mycophenolate mofetil 2 g/day, mycophenolic acid 1.44 g/day orally)[55,56];
- *Methotrexate* (5 mg to 12.5 mg, once a week subcutaneously or intramuscularly).[57]

In the case of prescribed low-dose methotrexate to older patients, a careful biologic and clinical monitoring is recommended to avoid toxic complications, in particular, related to renal insufficiency and leucopenia (4.52 ± 0.91).

In an RCT on 300 BP patients, the first-line use of methotrexate (10–12.5 mg weekly) combined with superpotent topical CS for the first month after initiation of therapy allowed a reduction in the 9-month relapse rate from 42% to 25% relative to topical CS alone.[58]

- *Ciclosporin* (3–5 mg/kg/day).[59] Based on the current lack of evidence for its efficacy and the potential adverse effect profile, including nephrotoxicity, high blood pressure and neurotoxicity, the use of ciclosporin is not recommended (4.90 ± 1.82).

Biologics Biologics may be considered in the few difficult-to-treat cases of BP according to the clinical features and course, response or contraindications to standard therapies as either add-on therapy or monotherapy (4.95 ± 0.46). They target pro-inflammatory key cytokines and cellular functions that contribute to tissue damage in BP. It must be underlined that there is still no strong evidence supporting their use, which is therefore not validated and may not be reimbursed.

- For *B-cell depletion therapy with anti-CD20 monoclonal antibody* (mAb) using rituximab, it is recommended to apply either the rheumatoid arthritis protocol (two 1 g intravenous infusions, 2 weeks apart) or the lymphoma protocol (375 mg/m^2 intravenous infusion, once weekly for 4 weeks) (4.66 ± 0.70). The beneficial effect of rituximab in BP seems lower than in pemphigus in terms of control of disease activity, clinical remission and relapse risk. Potential severe side-effects in the debilitated elderly or as a result of an incidental COVID-19 infection should be kept in mind.[60–62]
- *Intravenous immunoglobulins* (level of evidence 1) (4.48 ± 0.65). In an RCT add-on therapy with intravenous immunoglobulin, 2 g/kg/day in BP cases with no improvement on prednisolone ≥0.4 mg/kg/day showed a trend towards a beneficial effect, which did not, however, reach statistical significance. Potentially severe side-effects in older patients especially the risk of acute renal failure must be underlined.[63]
- *Omalizumab*. Omalizumab is an anti-IgE mAb, which is approved in asthma and spontaneous idiopathic urticaria. Some limited open series have suggested the efficacy of omalizumab in BP patients. Omalizumab may be considered, in particular, in BP patients with urticarial inflammatory lesions and high serum IgE levels (4.52 ± 0.87). Omalizumab may also be considered in patients with neoplasia, which is a contraindication to most immunosuppressive drugs (4.56 ± 0.82).[64]
- *Dupilumab*. Dupilumab is an anti-IL-4 Rα mAb, which is approved in atopic dermatitis. It is off-label in BP (4.36 ± 0.86). An open retrospective series on 13 patients showed that 54% of patients achieved disease clearance, suggesting the potential efficacy of the drug. The drug was well tolerated.[65,66]
- New therapeutic approaches, including blockade of IL-17, IL-12/IL-23, IL-5Rα, eotaxin, neonatal Fc receptor and LTB4/C5aR, are currently being tested in BP (see update in: https://clinicaltrials.gov/ct2/results?cond=bullous+pemphigoid&term=&cntry=&state=&city=&dist=)

Indications of treatment depending on initial BP extent

Localized BP. Localized BP is defined by the presence of lesions involving one body site.

Initial treatment is based on topical clobetasol propionate 10 g per day, which is applied once daily over the involved area. It is recommended to continue treatment until 15 days after CDA followed by a progressive tapering of CS doses over 4 months (4.64 ± 1.11).

Mild and moderate BP (BPDAI score < 20 and BPDAI score ≥ 20 < 57, respectively).

It is recommended to define mild/moderate BP as the occurrence of 10 or less new blisters per day or by the presence of few non-bullous inflammatory lesions in different localizations. It is recommended to use the BPDAI scoring system; mild BP corresponds to a severity score lower than 20 points, and moderate BP corresponds to a BPDAI score < 57 points (4.76 ± 0.59).[69]

For the initial treatment of mild to moderate BP, different options are available. The final choice will depend on their availability, practical feasibility and presence of contraindications.