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Data availability: Further information is available on direct request to the corresponding author.

Treatment satisfaction, safety and effectiveness of adding methotrexate to adalimumab in patients with psoriasis responding suboptimally to adalimumab in a real-world setting

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Dear Editor, An inadequate response to biologics may reach 30% in patients with psoriasis.[1,2] In other inflammatory diseases, a positive effect of adding methotrexate (MTX) to adalimumab (ADA) has been reported.[3,4]

In this real-world, Canadian multicentre, single-arm, phase IIIb, open-label study, suboptimal responders who have been receiving ADA for ≥ 16 weeks, who had a Physician's Global Assessment (PGA) ≥ 3 and Psoriasis Area Severity Index (PASI) ≥ 5, continued to self-administer ADA (40 mg every other week). Oral MTX was added (10–25 mg per week as per investigator's decision and could vary throughout the study), as well as folic acid (1-mg tablet daily) for 24 weeks.

Aligned with guidelines emphasizing patient-centred care,[5] the primary endpoint was the proportion of suboptimal responders achieving a satisfactory response to treatment after 16 weeks, using a questionnaire including both investigator and patient assessments.[6] Achieving a satisfactory response was defined as investigator/patient being either highly satisfied or completely satisfied (Figure 1a). Secondary endpoints were PASI 50/75/90/100 (% of patients who achieved ≥ 50/75/90/100 reduction in PASI score from baseline), PGA response of clear or minimal, and Dermatology Life Quality Index (DLQI) score of 0 or 1. ADA serum concentrations were measured at trough (prior to administration of ADA and MTX), and treatment-emergent adverse events (TEAEs) were collected.

From 12 sites, 46 patients were enrolled: 93·5% (43 of 46) completed the study, and no patients discontinued due to an AE, consent withdrawal, or were lost to follow-up. Their mean age (SD) was 46·5 (12·2) years, and their median duration of psoriasis (Q1, Q3) was 20·2 (13·8, 30·0) years. The majority was male (76·1%) and white (76·1%), with a mean body mass index of 32·1 (6·5) kg m^{-2}.

At baseline as assessed by investigators and patients, respectively, no patients (0/46) and 15·2% [7 of 46; 95% confidence interval (CI) 4·8–25·6%] reached a satisfactory response with treatment, i.e. score ≥ 4 on a 1–5 scale. At week 16, these proportions increased, respectively, to 50·0% (23 of 46; 95% CI 35·6–64·4%) and 47·8% (22 of 46; 95% CI 33·4–62·3%), reaching 56·5% (26 of 46; 95% CI 42·2–70·8%) and 54·3% (25 of 46; 95% CI 40·0–68·7%) by week 24 (Figure 1a).

Treatment effectiveness was significantly different from baseline to weeks 8, 16 and 24 ($P < 0·001$) (baseline PASI score = 10·4; n = 46). From weeks 8 to 24, 43·5–65·2% of patients reached a PASI 50 response, 28·3–39·1% a PASI 75 response, 13·0–28·3% a PASI 90 response, and 13·0–26·1% a PASI 100 response (Figure 1b). Patients achieving a PGA clear or minimal increased from 26·1% to 43·5% between weeks 8 and 24, which was significantly different from baseline ($P < 0·001$) (Figure 1c). DLQI of 0 or 1 was achieved numerically by 20% of patients at week 8, plateauing at 37% by week 16.

Overall, results from ADA serum concentration suggest higher concentrations in patients achieving a PGA response of clear or minimal and a DLQI score of 0 or 1, than in patients who did not (Figure 1d). The highest concentrations were measured in patients achieving PASI 90 and PASI 100, varying from 6·4 to 9·3 μg mL^{-1}, while serum concentrations in patients who did not achieve response were between 3·6 and 4·0 μg mL^{-1}.

A proportion of 58·7% (27 of 46) experienced at least one TEAE. Patients with at least one TEAE reasonably or possibly related to ADA or MTX represented 4·3% and 15·2%, respectively (n = 46). No deaths were reported during the study. One patient (2·2%) experienced serious AEs (loss of consciousness, cardiac arrest, tonic–clonic seizure and hypercapnia), considered by the investigator not reasonably or possibly related to ADA or MTX. The patient was prematurely discontinued from the study due to poor adherence to the protocol.

The sharp increase from baseline in satisfaction with treatment and its maintenance over 24 weeks are key findings in this study.[7] The PASI 100 responses and the PGA responses clear or minimal suggest a need to assess whether the proportion of patients achieving a better skin clearance could

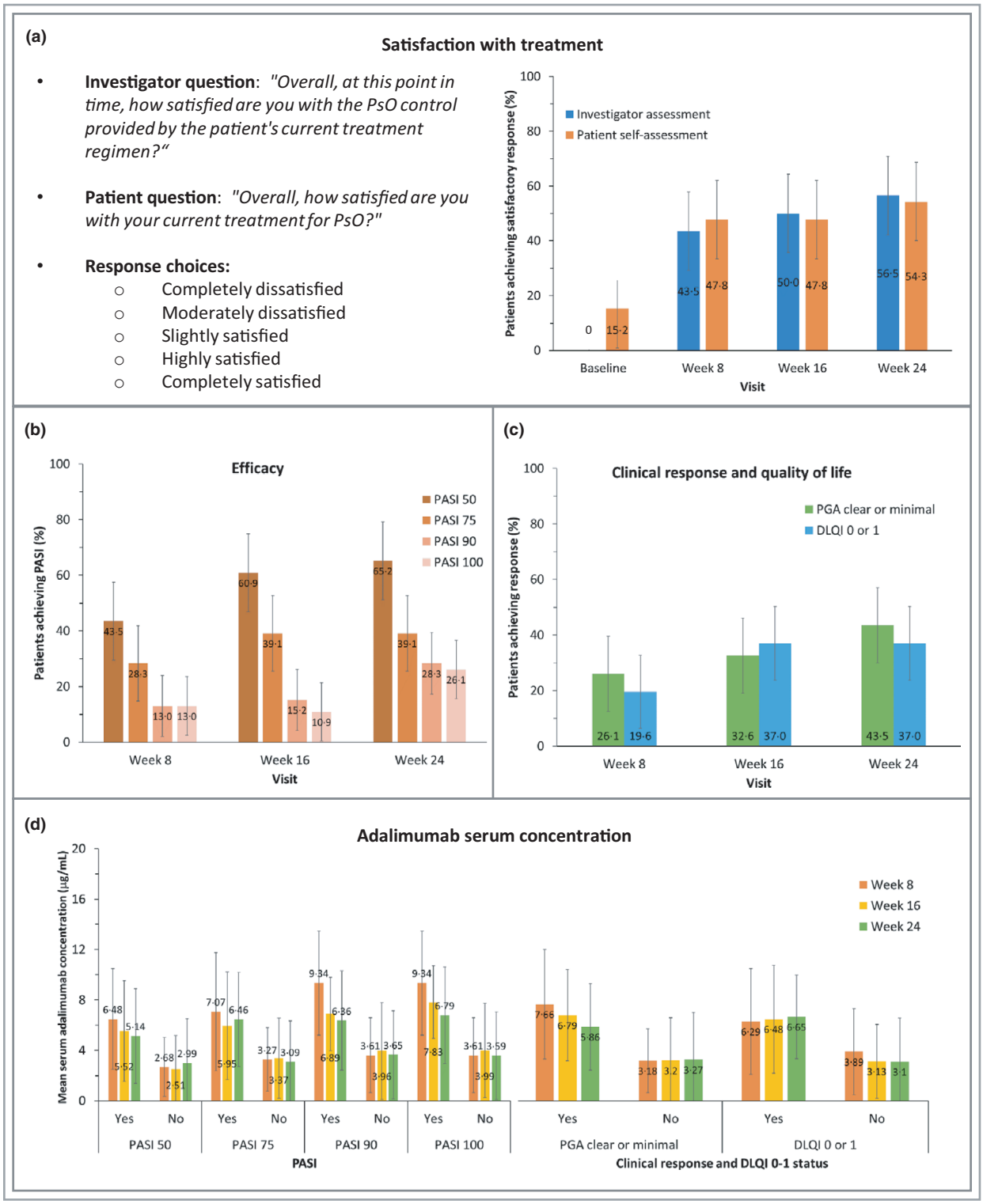

Figure 1 Impact of adding methotrexate to an adalimumab therapy in patients with psoriasis. (a) Satisfaction questions, response choices and satisfaction with treatment at baseline and weeks 8, 16 and 24 for investigator assessment and patient self-assessment; satisfaction achieved defined as highly satisfied or completely satisfied. (b) PASI responses at weeks 8, 16 and 24. (c) PGA clear or minimal; DLQI score of 0 or 1 at weeks 8, 16 and 24. (d) Adalimumab concentration at weeks 8, 16 and 24: PASI responses, PGA clear or minimal response, and DLQI score of 0 or 1 response. Bars show 95% CIs, except for adalimumab concentrations, shown with SD. Proportions are shown for the nonresponder imputation analysis. Similar results were obtained with a last-observation-carried-forward analysis, used for sensitivity. PsO, psoriasis; CI, confidence interval; PASI, Psoriasis Area Severity Index; PGA, Physician's Global Assessment; DLQI, Dermatology Life Quality Index.

improve beyond week 24. Limitations of the study include a slower-than-expected enrolment – possibly because ADA monotherapy was the preferred approach of Canadian dermatologists to treat psoriasis – and the single-arm study design as each participant served as their own control, and outcomes after addition of MTX are compared with similar assessments at baseline. The variability in MTX dosing based on investigator judgement may have been another limitation.

In a real-world setting over 24 weeks, adding MTX to ADA increased treatment satisfaction, effectiveness and quality of life in patients with psoriasis suboptimally responding to ADA monotherapy. No new safety signals were detected.

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Conflicts of interest: see Appendix S1S1 for full statement.

Data availability: AbbVie is committed to being transparent regarding the clinical trials sponsored by sharing data from and information about clinical trials (https://vivli.org/).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Full conflicts of interest statement.

Bullous pemphigoid after SARS-CoV-2 vaccination: spike-protein-directed immunofluorescence confocal microscopy and T-cell-receptor studies

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Dear Editor, Growing evidence suggests that SARS-CoV-2 vaccination is associated with a variety of cutaneous reactions. These include autoimmune-mediated conditions such as autoimmune blistering diseases (AIBDs), one of which is bullous pemphigoid (BP).[1,2] We report new-onset BP in two patients following their first SARS-CoV-2 vaccination.

The first patient was an 80-year-old man who noticed reddish itchy macules with small blisters on his lower legs 1 week after vaccination with BTN162b2.[2] Two weeks later, after he had received his second shot, these erythematous/bullous lesions spread over his trunk (Figure 1a). The second patient was an 89-year-old man who noticed 2 days after the first BTN162b2 vaccination itchy erythematous/bullous lesions on his entire integument. Neither of the patients reported intake of any new medications or other newly diagnosed conditions prior to the AIBDs.

In both cases, subepidermal clefts were demonstrated on routine histology (Figure 1b). In both patients, direct immunofluorescence on frozen sections revealed linear deposits of IgG and C3 at the basement membrane zone. Indirect immunofluorescence showed bandlike IgG deposits on the epidermal side in both patients. In both cases, enzyme-linked immunosorbent assay revealed highly elevated autoantibody levels against BP-180 (365 U mL^{-1} and 115 U mL^{-1}, normal