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Severe atopic dermatitis and dupilumab

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The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct, and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.

QUESTION

Is there an indication for the drug dupilumab in the treatment of severe atopic dermatitis? Is its constant use effective and safe?

METHODS

Eligibility criteria

The eligibility criteria used to select the evidence and data were as follows: patients with severe atopic dermatitis (refractory to conventional treatment); intervention: dupilumab; comparison: placebo; outcomes: reduction of the effects of the disease and adverse events; study design: randomized clinical trials and no period and language restriction.

Base consulted and strategy used

Searches were performed in the Medline database via PubMed, using the following search strategy: (Dermatitis, Atopic OR Atopic Dermatitides OR Atopic Dermatitis OR Atopic Neurodermatitides OR Atopic Neurodermatitis OR Disseminated Neurodermatitides OR Disseminated Neurodermatitis OR Atopic Eczema) AND (dupilumab) AND Random*.

Extracted data

The studies selected according to the eligibility criteria had their full texts accessed, from which the following variables were extracted: author's name, year of publication, study design, description of the population, intervention, comparison, outcomes, and follow-up time.

Risk of bias

The biases evaluated were: randomization and allocation methods, double and rater blinding, losses, appropriate outcomes, prognostic characteristics of the compared groups, ITT analysis, presence of sample calculation, early interruption, selection bias, and "confounding bias." This risk was estimated as very high, high, or low.

Quality of evidence analysis by outcome

The quality of evidence analysis was expressed as very low, low, moderate, and high. The items considered (using GRADEpro software) were classified as very high, high, and low, using the items: risk of bias, inconsistency, precision, indirect evidence, and publication bias.

Expression of results (with meta-analysis)

Event risk difference (difference between absolute risk of intervention and comparison for each outcome) and 95% confidence interval (CI) for each risk difference are presented. Heterogeneity in I^2 ranges from 0 to 100%, with values above 50% considered high (inconsistency). Random (I^2>50%) and fixed (I^2≤50%) models were used for analysis. Sensitivity analysis was used to treat I^2 >50% in the presence of publication bias (Egger's test).

RESULTS

Works retrieved and selected

A total of 1,344 works were retrieved, of which 57 publications were selected by title and/or abstract. Nine randomized

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clinical trials were included to support the analyses and conclusions of this review[1-9].

A total of 2,606 patients submitted to dupilumab and 1,441 submitted to placebo were analyzed. The populations are children, adolescents, and adults. The dupilumab regimen used was a 300 mg subcutaneous injection once every 1, 2, or 4 weeks. The follow-up time ranged from 12 to 28 weeks. The outcomes analyzed were: Eczema Area and Severity Index (EASI) 75 and 50 (improvement ≥50% and 75%); Investigator's Global Assessment (IGA) (0–1 and/or improvement ≥2 points); numerical rating scale (NRS) pruritus (reduction ≥3 points); and treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Subgroup analysis by age was not performed due to the homogeneity obtained, as well as the fact that 80% of the studies were in adults.

FLUX DIAGRAM

Selection of retrieved works in the virtual databases of scientific information is detailed in Figure 1.

RESULTS BY OUTCOMES

EASI 50 (improvement ≥50%)

In this analysis (Figure 2), 1,773 patients submitted to dupilumab and 1,684 to placebo were studied. Treatment with dupilumab increases the improvement by ≥50% (EASI 50) by 40% (95%CI 37–43%) (NNT: 2) when compared to placebo. The quality of evidence is high.

EASI 75 (improvement ≥75%)

In this analysis (Figure 3), 2,606 patients submitted to dupilumab and 2,615 to placebo were studied. Treatment with dupilumab increases the improvement by ≥75% (EASI 75) by 37% (95%CI 34–39%) (NNT: 3) when compared to placebo. The quality of evidence is high.

IGA (0–1 and improvement ≥2 points)

In this analysis (Figure 4), 2,606 patients submitted to dupilumab and 2,615 to placebo were studied. Treatment with

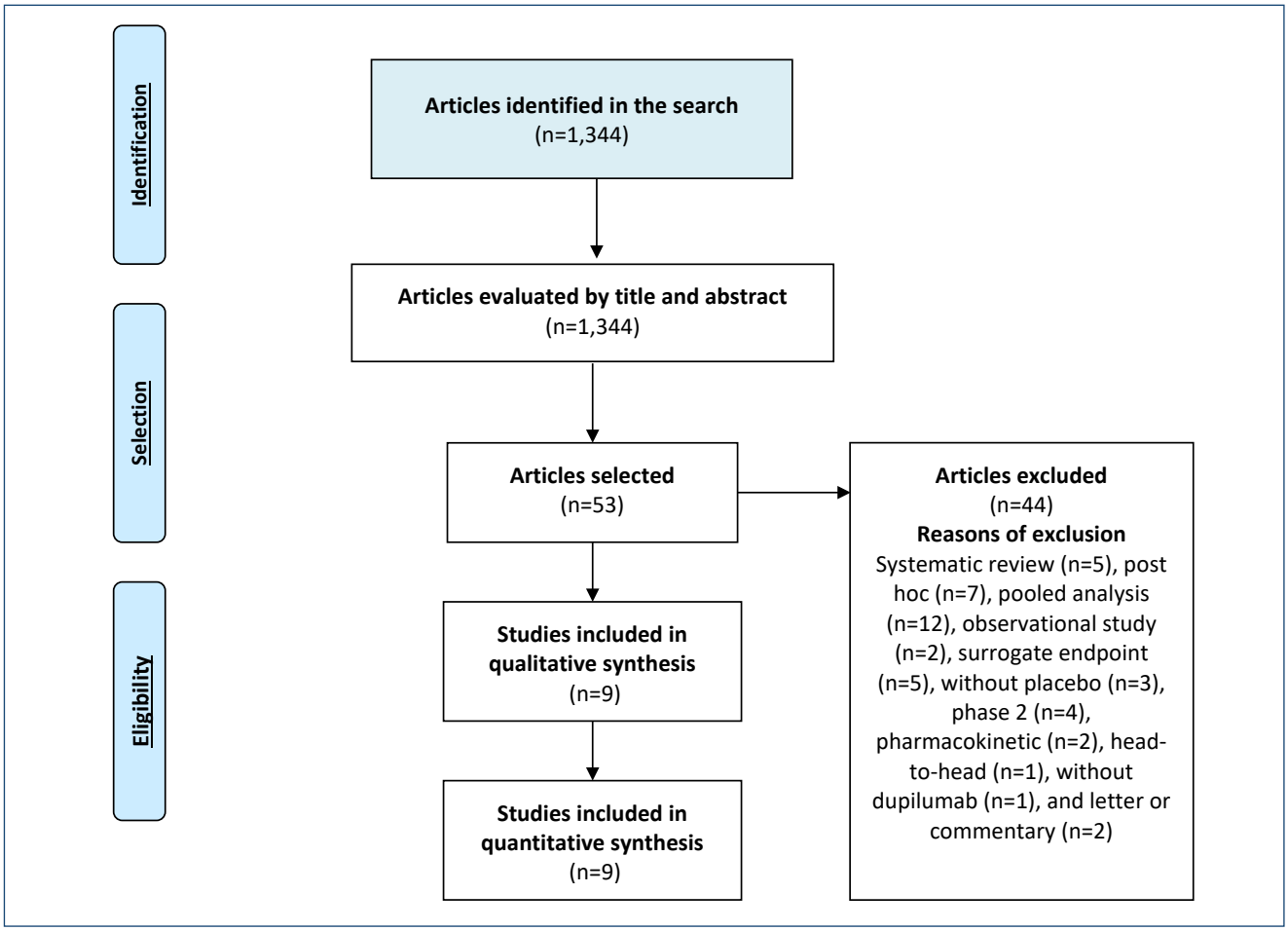

Figure 1. Flow diagram of evidence retrieved, selected, and included, with exclusion reasons.

dupilumab increases the improvement measured by IGA by 25% (95%CI 23–27%) (NNT: 4) when compared to placebo. The quality of evidence is high.

NRS pruritus (reduction ≥3 points)

In this analysis (Figure 5), 2,126 patients submitted to dupilumab and 1,931 to placebo were studied. Treatment with dupilumab reduces pruritus measured by the NRS by 21% (95%CI 5–36%) (NNT: 5) when compared to placebo. The quality of evidence is low.

Treatment-emergent adverse events

In this analysis (Figure 6), 748 patients submitted to dupilumab and 664 to placebo were studied. There is no difference in the risk of TEAEs with dupilumab treatment compared to placebo. The quality of evidence is high.

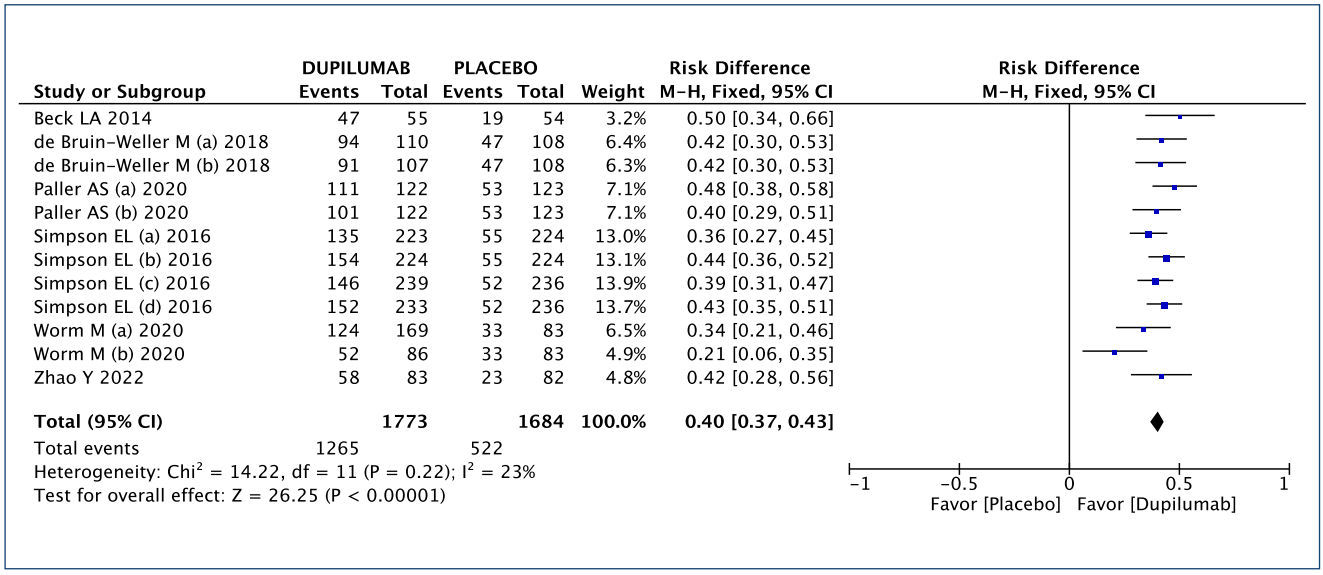

Figure 2. Analysis of the Eczema Area and Severity Index 50 outcome in patients with severe atopic dermatitis treated with dupilumab.

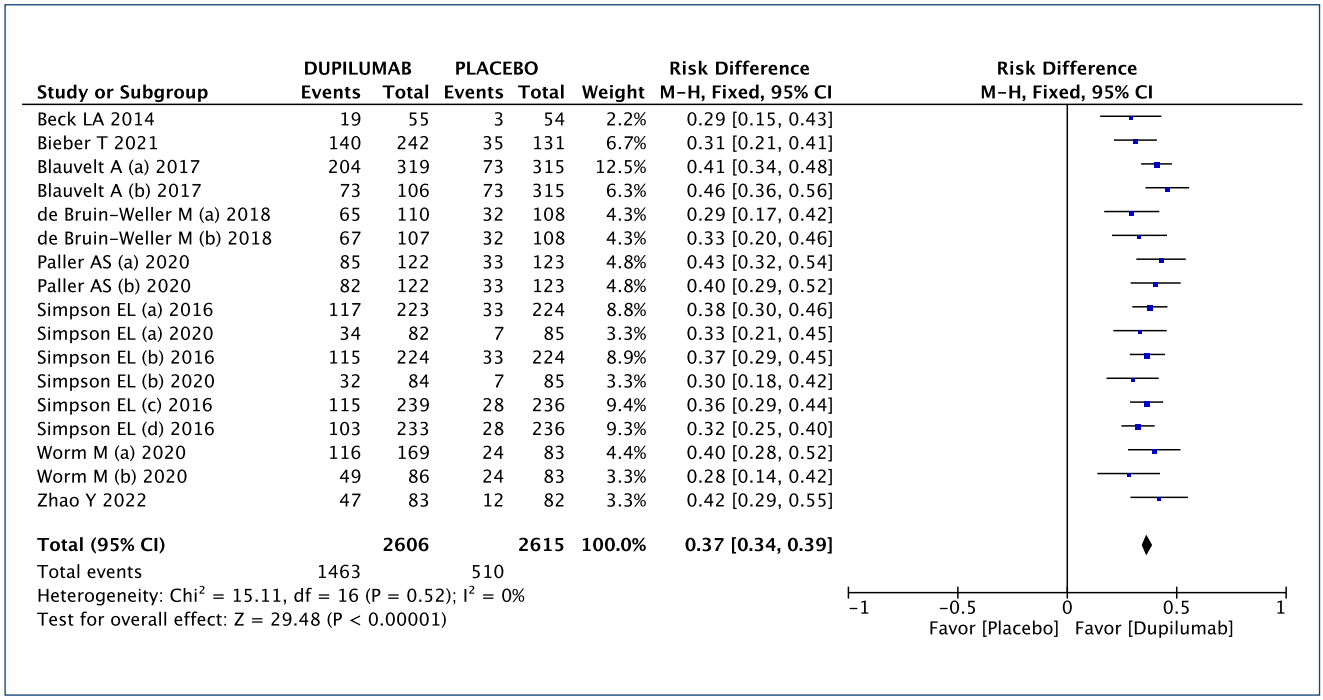

Figure 3. Analysis of the Eczema Area and Severity Index 75 outcome in patients with severe atopic dermatitis treated with dupilumab.

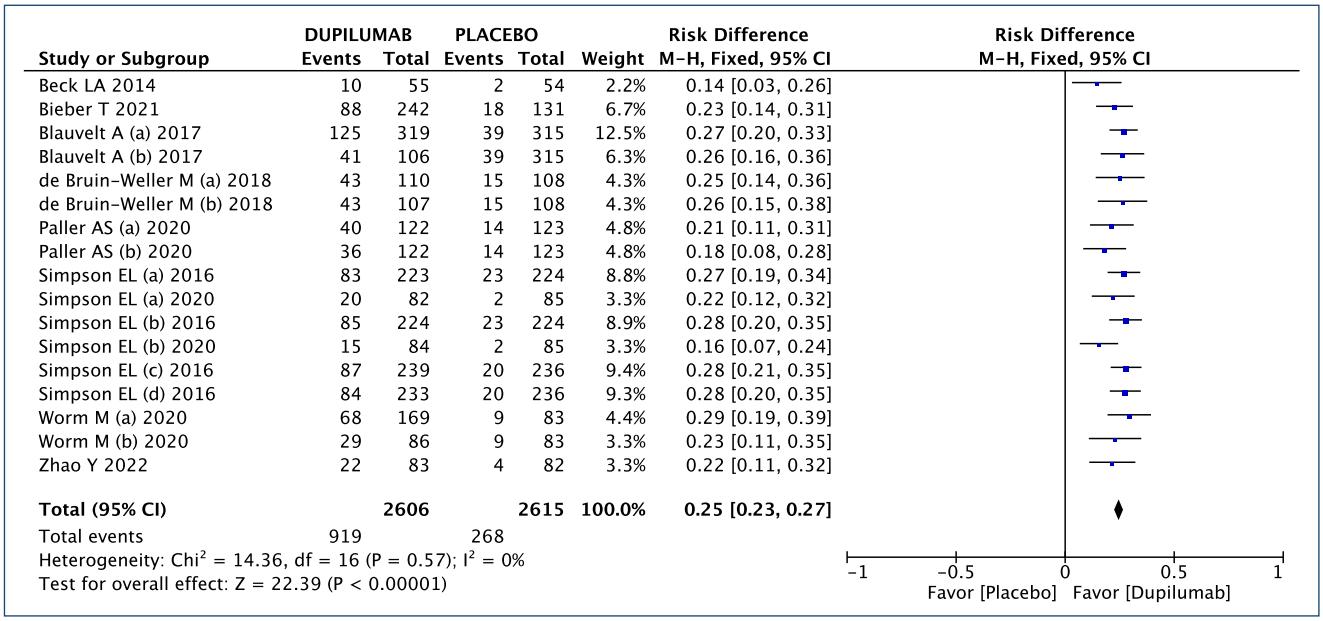

Figure 4. Analysis of the Investigator's Global Assessment outcome in patients with severe atopic dermatitis treated with dupilumab.

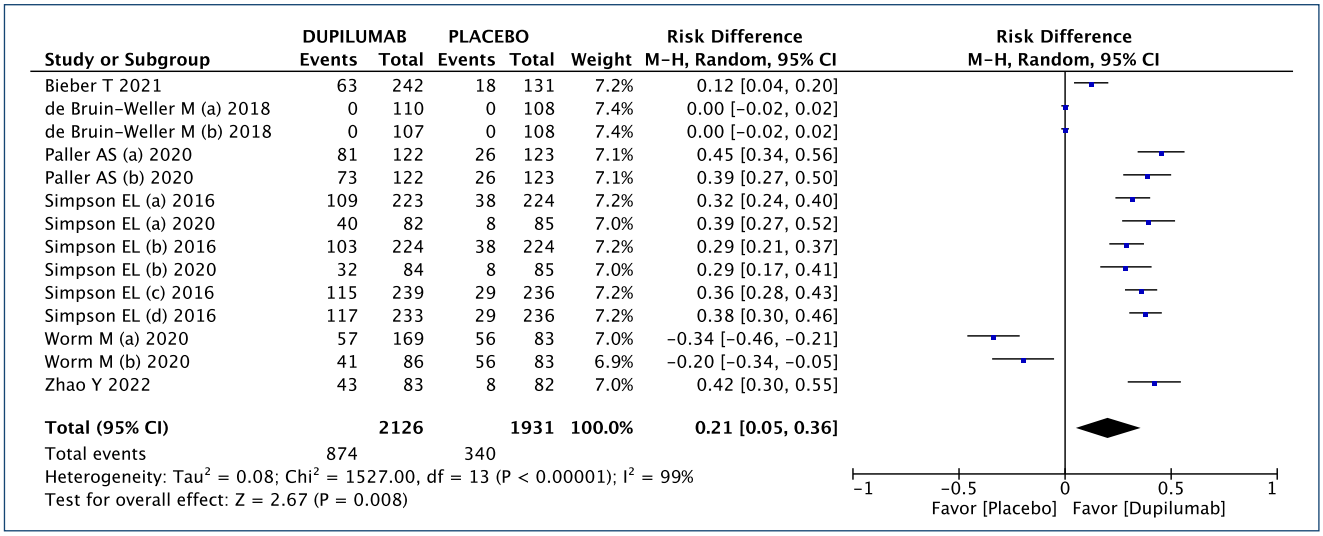

Figure 5. Analysis of the pruritus numerical rating scale outcome in patients with severe atopic dermatitis treated with dupilumab.

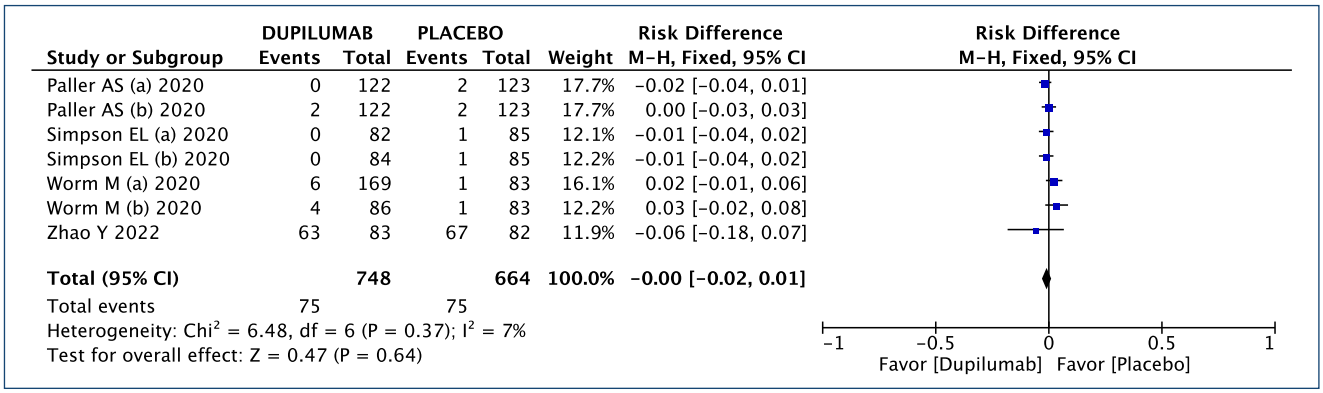

Figure 6. Analysis of treatment-emergent adverse events in patients with severe atopic dermatitis treated with dupilumab.

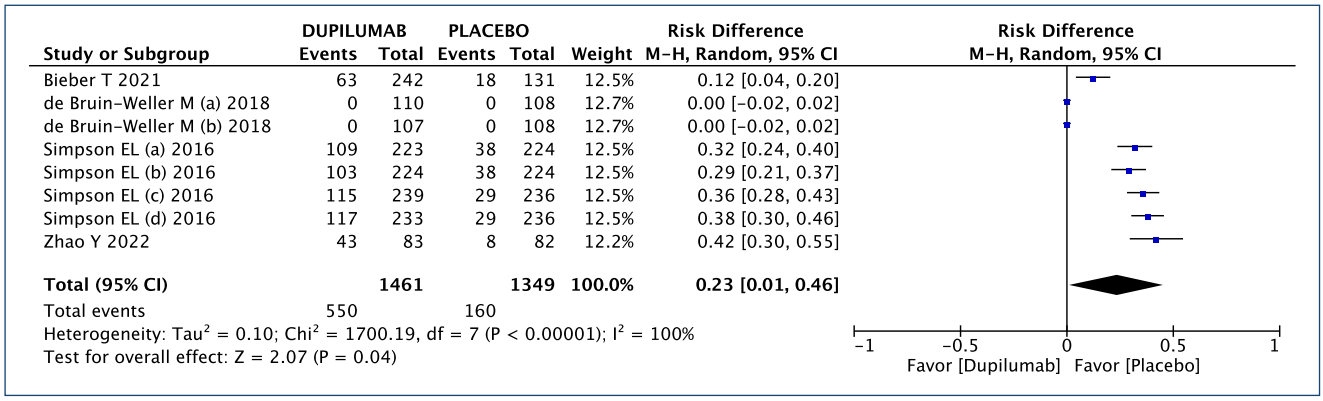

Figure 7. Analysis of serious adverse events in patients with severe atopic dermatitis treated with dupilumab.

Serious adverse events

In this analysis (Figure 7), 1,461 patients submitted to dupilumab and 1,349 to placebo were studied. Treatment with dupilumab increases the risk of serious adverse events by 23% (95%CI 1–46%) (NNH: 4) when compared to placebo. The quality of evidence is low.

SUMMARY OF EVIDENCE

The treatment of patients with severe atopic dermatitis using dupilumab at the usual doses, and with an average follow-up of 6 months, produces benefits (EASI 50/75, IGA, NRS outcomes), with an increased risk of SAEs.

AUTHORS' CONTRIBUTIONS

WB: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **LSB:** Supervision, Validation, Visualization, Writing – review & editing. **RSS:** Supervision, Validation, Visualization, Writing – review & editing. **JHB:** Supervision, Validation, Visualization, Writing – review & editing.

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