Psoriasis in moderate grave plaque - immunobiological treatment

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Final version: *July 1, 2018*

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http://dx.doi.org/10.1590/1806-9282.65.4.493

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

INTRODUCTION

Immunobiological agents are recombinant, genetically engineered proteins, which may be monoclonal antibodies, fusion proteins or recombinant human cytokines. Its action is to block, neutralize or antagonize specific targets of the inflammatory process.

METHOD

A systematic review of the literature was carried out, with the descriptors according to PICO, where P corresponds to patients with moderate to severe plaque psoriasis, I as in intervention with etanercept, infliximab, adalimumab, ustekinumab, guselkumab, ixekizumab, secukinumab and O as in outcome, effectiveness and safety. The search to answer the clinical doubts was carried out in the Medline-PubMed database, and for each of them an evidence search strategy was prepared:

3.1. Psoriasis AND (itolizumab OR brodalumab OR secukinumab OR tildrakizumab OR ixekizumab OR guselkumab OR Briakinumabe OR Tofacitinib OR Certolizumab OR etanercept OR TNFR-Fc fusion protein OR Enbrel OR Receptors, Tumor Necrosis Factor OR infliximab OR monoclonal antibody OR monoclonal antibodies OR Remicade OR MAb cA2 OR adalimumab OR Humira OR ustekinumab OR Stelar OR immunobiological therapy) AND random* Psoriasis AND (acitretin OR neotigason) AND random*

- Psoriasis AND (etanercept OR TNFR-Fc fusion protein OR Enbrel) AND random*
- Psoriasis AND (infliximab OR Remicade OR MAb cA2) AND random*
- Psoriasis AND (adalimumab OR Humira) AND random*
- Psoriasis AND (ustekinumab OR Stelara) AND random*
- Psoriasis AND Guselkumab AND random*
- Psoriasis AND Ixekizumab AND random*
- Psoriasis AND Tildrakizumab AND random*
- Psoriasis AND (itolizumab OR brodalumab OR

secukinumab OR tildrakizumab OR ixekizumab OR guselkumab OR Briakinumabe OR Tofacitinib OR Certolizumab OR etanercept OR TNFR-Fc fusion protein OR Enbrel OR Receptors, Tumor Necrosis Factor OR infliximab OR monoclonal antibody OR monoclonal antibodies OR Remicade OR MAb cA2 OR adalimumab OR Humira OR ustekinumab OR Stelar OR immunobiological therapy) AND random*

The eligibility criteria are non-randomized studies with weak evidence strength, non-PICO related studies, articles in languages other than Portuguese, English or Spanish. Recovered evidence was selected from the critical evaluation using discriminatory instruments (scores): JADADe GRADE for Randomized Clinical Trials and New Castle Otawa scale for observational studies.

RESULTS

In which conditions treatment with immunobiology is indicated?

Indications for the use of immunobiologicals in patients over 18 years of age with moderate to severe plaque psoriasis with a PASI score above 10 to 12 or a compromised body surface area of more than 10% are:

- Patients with failure to respond to treatment, or contraindications, or intolerance to at least one of the systemic treatments or phototherapy performed in adequate dose and sufficient time[1-36]**(A)**.
- Treatment failure is considered to be less than 50% improvement in PASI pre-treatment or improvement of less than 75% relative to PASI pre-treatment associated with a significant impact of the disease on quality of life measured by DLQI (Dermatology Life Quality Index) >= 10.

Some groups of patients with moderate to severe plaque psoriasis have not been studied for immunobiological treatment[1-36]**(A)**.

- Patients with associated infections or use of antibiotics in the last week before the beginning of the study;
- Patients with other associated skin conditions, in addition to guttate, erythrodermic, or pustular psoriasis;
- Patients with hematological, renal and/or hepatic dysfunction;
- Patients with a history of cancer of any etiology in the last 5 years;

Treatment with PUVA in the last 4 weeks, or topical corticosteroids, vitamin A or D analogues, dithranol or UVB phototherapy in the last 2 weeks; or use of any immunobiological or anti-TNF antibody at any time prior to the beginning of the study;

Pregnant women or patients with intentions of pregnancy.

RECOMMENDATIONS

Indications for the use of immunobiological drugs in patients over 18 years of age with moderate to severe plaque psoriasis with a PASI score above 10 or a compromised body surface area of more than 10% are the non-responsive to systemic or phototherapeutic treatment, contraindications, or intolerance to at least one of the systemic treatments or phototherapy performed in adequate dose and sufficient time.

What is the effectiveness and what is the risk of ethanercept in the treatment of psoriasis?

Involving 121 patients over 18 years of age, with moderate to severe psoriasis, with involvement of more than 10% of the body surface or more than 30% of the scalp; study allocated 59 patients on etanercept, subcutaneous use, 50mg twice weekly for one week, followed by 50mg once a week for 12 weeks and compared with 62 patients on placebo, subcutaneously, twice weekly for one week, followed by once a week for 12 weeks. The proportion of patients who responded with PASI 50/75/90 at the end of 12 weeks of follow-up were significantly higher in the intervention group, using ethanercept, (78% had PASI 50, NNT=2, p<0.001, 54% had PASI 75, NNT=2, p <0.001; 23% had PASI 90, NNT=5, p<0.001). At the 24-week assessment, the proportion of patients achieving PASI 50/75/90 were similar in the intervention and comparison groups. Adverse effects occurred in the first 12 weeks of follow-up, 54.2% of patients taking etanercept and 54.8% of patients on placebo, with no deaths or serious effects. The most commonly described were application site infection, arthralgia and headache[1]**(A)**.

Another study selected 350 patients with clinical diagnosis of plaque psoriasis for more than 6 months, stable in the last 2 months, with a compromise of more than 10% of the body surface area, with an overall evaluation performed by the physicians (PGA) at least moderate (≥ 3) and PASI ≥ 12. They were divided into three different groups, group A be-

ing 139 patients treated with briakinumab 200mg, subcutaneously at weeks 0 and 4, followed by 100mg at week 8; group B with 139 patients treated with etanercept 50mg, subcutaneously twice weekly, 3 to 4 days apart, for 12 weeks and 72 patients in group C on placebo[3](A).

Of the patients treated with briakinumab, 72.7% achieved PGA 0/1 at week 12 of evaluation, compared to 29.5% of etanercept-treated patients and 4.2% of placebo patients (p <0.001 in both comparisons). Of the patients treated with briakinumab, 80.6% achieved a PASI 75 response at week 12, compared to 39.6% of patients on etanercept and 6.9% of patients on placebo (p <0.001 in both comparisons). Serious adverse events were reported in 2 patients (1.4%) of patients in group A, one patient in group B (0.7%) and two patients (2.8%) in group C[3](A).

Patients (n = 142) with moderate to severe plaque psoriasis, involving more than 10% of the body surface area, with a PASI score of at least 10, stable, with failure to respond or contraindications or intolerance to at least one of the systemic or phototherapy treatments performed at adequate dose and sufficient time, were randomized, being 96 patients on etanercept 50mg once a week and 46 patients on placebo once a week. Thus, 36 patients (37.5%) from the etanercept group and 1 patient (2.2%) from the placebo group presented PASI 75 response at the end of 12 weeks (p<0.0001) and PASI 90 response in 13 patients of the intervention group (13.5%) and 1 (2.2%) in the comparison group (p <0.05). The mean percentage of improvement in PASI compared to the start of treatment was 55.4% for the intervention group and 9.4% for the comparison group (p<0.0001). The difference in lesions lightening through the PGA was 34.2% for the group that performed etanercept (38.5% vs. 4.3%, p<0.0001). And the mean difference for improvement in quality of life through the DLQI score was 49.2% for the etanercept group (p<0.0001). The adverse effects reported with significant difference between the groups, with the highest number in the intervention group, were migraine (p=0.04) and influenza-like syndrome (p=0.03). The other signs and symptoms did not present a statistically significant difference[4](A).

Authors evaluated 583 patients who were allocated to 2 intervention groups: 196 patients for the use of etanercept 50 mg per week and 194 patients for the use of etanercept 50 mg twice a week and 193 patients on placebo. There was a statistically significant difference for the use of etanercept compared to placebo, both for once a week use (46%, p<0.0001, NNT=3) and twice a week (51%, p<0.0001, NNT=2) in the intervention group, and for the DLQI quality of life assessment at the end of 12 weeks[5](A).

Another study has included patients for the use of etanercept 25 mg per week (n = 160), 50 mg per week (n=162) or 50 mg twice a week (n=164) and compared with placebo use (n=166). There was a significant improvement in quality of life, based on a minimum reduction of 5 points in the DLQI score, in patients who used etanercept at all different doses in relation to placebo, improvement of 22% for etanercept 25mg once a week, in 26% with 50mg once a week, 35% with 50mg twice a week (p <0.0001 in all groups, with NNT=5, NNT=4 and NNT=3, respectively). For the score of 5 to 14 points in the DLQI, there was significant improvement for both the use of etanercept 50mg once or twice a week (p<0.05)[6](A).

Of the 611 patients selected for the study, 194 received etanercept 50 mg twice a week and another group of 196, etanercept 25 mg twice a week; compared with 193 patients on placebo. There was a statistically significant difference between the use of etanercept versus placebo in the reduction to PASI 75, from 43% to etanercept 50mg twice a week and 29% to etanercept 25mg twice a week (p<0.0001, NNT=3 and NNT=4, respectively). There was also a statistically significant difference (p<0.0001) for PASI 50 (68% for 50mg, NNT=2 and 55% for 25mg, NNT=2) and PASI 90 (20% for 50mg, NNT=2 and 10% for 25mg, NNT=10); and for the physician's global evaluation as to lightening of lesions (53% for 50mg, NNT=2 and 35% for 25mg, NNT=3, p <0.0001). Adverse events reported in the first 12 weeks of evaluation were injection site reaction, respiratory infection, headache, influenza-like syndrome, and all without any difference between the intervention and comparison groups[7](A).

Another 112 patients with similar characteristics were included in the study, and treatments with PUVA or systemic treatment should not have been performed in the last four weeks prior to the beginning of the study; UVB phototherapy, the use of topical corticosteroids, vitamins A and D analogues or anthralin should not have been used in the last two weeks. In the evaluation for PASI 75 there was a significant improvement regarding the use of etanercept in 28% (95% CI 16% to 40%, p<0.001, NNT=4). The percentage of patients reporting adverse events was similar in the

intervention and comparison groups, with the most frequent being the injection site reaction[8]**(A)**.

In another study involving 652 patients with psoriasis, 160 received a low dose of etanercept (25 mg once a week), 162 received an intermediate dose of etanercept (25 mg twice a week), and 164 patients received a high-dose of etanercept (50 mg twice a week), compared with 166 patients on placebo. In the evaluation at the end of week 12, there was a significant improvement in the treatment for all doses of etanercept for PASI 50 (27%, 44% and 60%, respectively, p<0.001), and for PASI 75 (10%, 30% and 45% respectively, p<0.001); for PASI 90 there was a significant improvement for the intermediate doses and high doses of etanercept (11% and 21% respectively, p<0.001). There was also a significant improvement in the total or almost total lightening of the lesions at the end of 12 weeks with all the different doses of etanercept (18%, 29% and 44%, p<0.001). The most frequently reported adverse events were injection site reaction, headache and respiratory infection, with no difference between groups[9]**(A)**.

RECOMMENDATIONS

Treatment with etanercept for moderate to severe plaque psoriasis during the 12-week period after no response to other systemic or phototherapy psoriasis treatment was effective for PASI 75 response evaluation and safe with mild to moderate adverse events, especially at the injection site, for doses of 25 mg once a week, 25 mg twice a week or 50 mg twice a week, with the best responses at higher doses of etanercept, which may vary from 10-28% 26-39.6% and 35-54%, respectively (table 1).

What is the efficiency and what is the risk of infliximab in the treatment of psoriasis?

With 835 patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy with PASI of at least 12 or involvement of at least 10% of the body surface, with no history of severe infection, lymphoproliferative disease, or active tuberculosis; the study randomized 627 patients on infliximab 3mg/kg or 5mg/kg on weeks 0, 2 and 6. The comparison was made with 208 patients on placebo. At week 10, patients on infliximab 3 and 5 mg/kg showed a significant improvement in DLQI scores compared to placebo (8.9 and 9.9, respectively, p<0.001)[11]**(A)**.

A group of 301 patients on intravenous infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks up to week 46, and a comparison group with 77 patients on placebo at weeks 0, 2, 6, 14 and 22, were submitted to the study and then cross over was performed for the use of infliximab. There was a significant improvement of PASI in the 10th week of evaluation in patients using infliximab, 79.6% had a PASI 75 response (NNT=2, p<0.001) and 55.8% had a PASI 90 response (NNT=2, p<0.001). Regarding the DLQI score, there was also a significant improvement for the use of infliximab of 9.9, p<0.001)[13]**(A)**.

TABLE 1. EVALUATION OF THE ETANERCEPT EXPRESSED BY THE ESTIMATED BENEFIT IN PERCENTAGE.

Author	Dose	Follow-up Time	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PGA (%)	DLQI (%)
Bagel J[1]	100mg/week	12 weeks	78	54	23		
Gottlieb AB[3]	50mg/week.	12 weeks		39.6		29.5	
Van de Kerkhof[4]	50mg/week.	12 weeks		37.5		38.5	49.2
Krueger GG[5]	50mg/week.	12 weeks		46			
Feldman ST[6]	25mg/week.	12 weeks		22			
Feldman ST[6]	50mg/week.	12 weeks		26			
Feldman ST[6]	100mg/week.	12 weeks		35			
Pappa KA[7]	50mg/week.	12 weeks	55	29	10	35	
Pappa KA[7]	100mg/week.	12 weeks	68	43	20	53	
Gottlieb AB[8]	25mg/week.	12 weeks		28			
Leonard GL[9]	25mg/week.	12 weeks	27	10			18
Leonard GL[9]	50mg/week.	12 weeks	44	30	11		29
Leonard GL[9]	100mg/week.	12 weeks	60	45	21		44

Patients (n=249) over 18 years of age with a diagnosis of plaque psoriasis over the past 6 months, previous treatment with PUVA or other systemic treatment for psoriasis were randomized, with 99 patients using intravenous infliximab 3mg/kg and 99 patients on infliximab 5 mg/kg treated at weeks 0, 2 and 6. The comparison consisted of 51 patients on placebo. The induction treatment with infliximab resulted in significant improvement in PASI evaluated by obtaining a PASI 50 response (62.2% for the use of 3 mg/kg and 75.4% for the use of 5mg/kg, NNT = 2 for both groups, p<0.001), obtaining of PASI 75 response (65.8% for the use of 3mg/kg and 82% for the use of 5mg/kg, NNT=2 for both groups, p <0.001) and PASI 90 response (45.5% for the use of 3mg/kg and 55.6% for the use of 5mg/kg, NNT=3 and NNT=2 respectively, p <0.001). There were also significant lightening in the physician's overall evaluation in both the group that used 3mg/kg (61.9% NNT=2, p<0.001) and for the group that used 5mg/kg (80.1% NNT=2, p<0.001). As for the safety of the use of infliximab, over 70% of patients in the intervention groups and more than 60% of the comparison group patients experienced adverse events, mostly mild to moderate, and the most frequent were the infusion reactions[14] **(A)**.

One study involved 33 patients aged 21-69 years with moderate to severe plaque psoriasis involving more than 5% of body surface area. The intervention was performed with 11 patients using infliximab 5mg/kg, 11 patients using infliximab 10mg/kg, at weeks 0, 2 and 6, and comparing with 11 patients on placebo. There was a significant improvement, evaluated by obtaining the PASI 75 response with the use of infliximab at week 10 (63.6% for the use of 5mg/kg and 54.5% for the use of 10mg/kg, both with NNT=2, p<0.05). The mean percentage of PASI improvement was significant (p<0.0003) for the use of infliximab at the two different doses from the second week of treatment. The reported adverse events were all mild to moderate[16] **(A)**.

RECOMMENDATIONS

The induction treatment with infliximab in moderate to severe plaque psoriasis during the 10-week period was effective by evaluating the PASI75 response (65.8-79.6%) and improvement of the quality of life by the DLQI score (8.9 to 9.9%), besides being safe, with few mild to moderate adverse events, mainly infusion reactions, at doses of 3mg/kg, 5mg/kg or 10mg/kg, at weeks 0, 2 and 6 (table 2).

What is the efficiency and what is the risk of adalimumab in the treatment of psoriasis?

In period A of a double blind, placebo-controlled study of 12 weeks, patients were randomized 4:1 to receive adalimumab 40 mg every two weeks (followed by a single dose of 80 mg) or placebo every two weeks. In the 12 following weeks, period B, open trial, all patients received adalimumab 40 mg every two weeks starting at week 13, followed by a single blinded dose at week 12 of adalimumab 80 mg or placebo (for patients receiving placebo or adalimumab at period A, respectively). In Period A, efficacy was analyzed for all randomized patients and safety for all patients who received ≥1 dose of the study drug. For the 425 patients in this study (87 placebo, 338 adalimumab), a higher percentage with adalimumab achieved a 75% reduction of baseline PASI score (PASI 75 response) at week 12: placebo 11.5% (10/87); adalimumab 77.8% (263/338; NNT=2, P<0.001). The obtaining of PGA response 0 or 1 (total or almost total lightening), was achieved at week 12 by 14.9% placebo (13/87) and 80.5% adalimumab (272/338, NNT=2, P<0.001). For patients receiving adalimumab at any

TABLE 2. EVALUATION OF INFLIXIMAB EXPRESSED BY THE ESTIMATED BENEFIT IN PERCENTAGE

Author	Dose	Follow-up time	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PGA (%)	DLQI (%)
Feldman SR[11]	3mg/kg	10 weeks					8.9
Feldman SR[11]	5mg/kg	10 weeks					9.9
Reich K[13]	5mg/kg	10 weeks		79.6	55.8		9.9
Gottlieb AB[14]	3mg/kg	10 weeks	62.2	65.8	45.5	61.9	
Gottlieb AB[14]	5mg/kg	10 weeks	75.4	82	55.6	80.1	
Chaudhari U[16]	5mg/kg	10 weeks		63.6			
Chaudhari U[16]	10mg/kg	10 weeks		54.5			

time during the study, treatment-emergent adverse events (AEs) were reported by 63.4%; the most common was infection of the upper respiratory tract (16.1%). Severe AEs were reported by 3.5% of the population receiving adalimumab and severe infectious AEs by 1.2%, which include pulmonary infection, pneumonia and tuberculosis - 2 (0.5%) patients each. There was 1 death (chronic heart failure)[17](A).

Authors involved patients over 18 years of age with moderate to severe psoriasis with 10% or more of body surface involvement and PASI score above 10. All patients had plaque psoriasis for at least 1 year and lesion stability for at least 2 months. The period without other treatments was 2 weeks for topical treatment and phototherapy, and 12 weeks for biological treatment. Patients were randomized to 3 groups: 108 patients for adalimumab (ADA), subcutaneously, 80mg at week 0, followed by adalimumab 40mg every 2 weeks, from week 1 to 15, and 110 patients for oral methotrexate (MTX) 7.5 to 25mg per week for 16 weeks. The comparison consisted of 53 patients for the use of placebo. After 16 weeks of follow-up, 79.6% of adalimumab-treated patients achieved a PASI 75 response, compared with 35.5% for the methotrexate-treated group and 18.9% for the placebo-treated group, which means 60.7% improvement for ADA (NNT=2, p<0.001) and 16.6% for MTX (NNT=6, p<0.05). There was a statistically significant improvement in complete improvement of the lesions (PASI 100) in patients treated with ADA (16.7%) compared to patients treated with methotrexate (7.3%) or in patients treated with placebo (1.9%). Regarding adverse events, 73.8% of patients in the ADA group, 81.8% in the MTX group, and 79.2% in the placebo group had at least one adverse effect. However, there was no statistically significant difference between the groups for infectious conditions, moderate to severe adverse events, and drug-related adverse events. Adverse events leading to interruption of the study were higher in the methotrexate group, mainly due to events related to hepatic dysfunction. There were no reports of tuberculosis or deaths during the study[18-20](A).

Patients with similar characteristics but with a PASI score above 12 (N=1212) received phototherapy with UVB or topical treatment for more than 2 weeks and for more than 4 weeks for prior treatment with PUVA or non-biological systemic treatment, 6 weeks for the use of efalizumab and 12 weeks for any other biological treatment. The intervention was performed with 814 patients on adalimumab 80mg at week 0, followed by adalimumab 40mg every 2 weeks from week 1 to 15. The comparison was made with 398 patients taking placebo from week 0 to week 15. There was a significant improvement, evaluated by the obtaining of the PSI 75 response, with a 64% difference for the use of adalimumab (p<0.001, NNT= 2). There were also significant differences for the PASI 90 and PASI 100 responses at the 16th week of 43% (NNT=3) and 19% (NNT=6) respectively (p<0.001 for both comparisons). Regarding quality of life, there was also a significant improvement in the DLQI score for the intervention group from the fourth week of treatment. Adverse events were significantly higher in ADA patients, especially upper respiratory tract infections (p=0.01)[21-23](A).

Recruited from 42 locations in Japan, 169 patients over 20 years of age with moderate to severe plaque psoriasis, diagnosed for more than 6 months, stable for more than 2 months. Body surface involvement was greater than 10% or PASI greater than 12 for all patients. Group 1 with 38 patients on adalimumab 40 mg every 2 weeks; group 2 with 43 patients taking adalimumab 80mg every 2 weeks at week 0, followed by adalimumab 40mg every 2 weeks from week 2; group 3 with 42 patients taking adalimumab 80mg every 2 weeks. Group 4 was the control with 46 patients on placebo. There was a significant difference for the use of ADA in all the different doses for PASI 75 response (57.9% for group 1, 62.8% for group 2 and 81% for group 3, and 4.3% for placebo group, NNT=2 for all groups), in addition to significant improvement for lightening assessed by PGA. Injection site reactions and liver changes were the most commonly reported adverse events in the intervention group[24](A).

The authors assigned 808 patients on adalimumab 80mg at week 0 followed by 40mg at week 1 at week 15, and 397 patients on placebo. At week 16, patients receiving adalimumab showed improvement and a significant increase in the PCS score (physical components summary), without improvement over the MCS score (mental components summary)[25](A).

Authors divided 148 patients, being: group 1 with 46 patients taking adalimumab 80mg at week 0, followed by 40mg weekly from week 1, group 2 with 50 patients on adalimumab 80mg at weeks 0 and 1, followed by 40mg per week from week 2; with 52 patients receiving placebo from week 0. At week 12, there was a significant difference of 49% for group 1 compared to placebo (NNT=2, p<0.001) and 76% for

group 2 (NNT=2, p<0.001) in the improvement assessed by the PASI 75 response. All adverse events were moderate to severe and had a similar frequency in all groups[26](A).

RECOMMENDATIONS

Adalimumab treatment in moderate to severe plaque psoriasis over the period of 12 to 16 weeks was effective by evaluating the PASI 75 response and improving quality of life through the DLQI score (49-81%) in the following therapeutic regimens: 40 mg every 2 weeks (PASI75 57.9-79.6%, PASI90 43%, PASI100 16.7-19% and PGA 80.5%); 80 mg at week 0 followed by 40 mg every 2 weeks (PASI75 62.8%); and 80 mg every 2 weeks (PASI75 81%), in addition to being safe, with few mild to moderate adverse events (Table 3)

What is the effectiveness and what is the risk of ustekinumab in the treatment of psoriasis?

A multi-center randomized, double blind, placebo-controlled study evaluating the efficacy and safety of ustekinumab 45 mg and 90 mg at 5-year follow-up. The study included four distinct periods: (i) placebo control (weeks 0-12); (ii) placebo crossover and active treatment (weeks 12-28); (iii) random setting of the dose range (weeks 28-52) and (iv) long-term extension (weeks 52-264), during which dose and/or dose interval adjustments were made by the investigator. Baseline randomization was stratified by research site, weight (≤90 kg or >90 kg) and if the patient did not have an inadequate response, intolerance or contraindication to less or more than three conventional systemic therapies. The second randomization, at week 28, was stratified by research site and baseline weight (≤ 90 kg or >90 kg). In the general population, 70% (849 of 1212) of ustekinumab-treated patients completed treatment by week 244, with better responses at doses of 45 and 90 mg. Improvement in the Severity Index (PASI 75 response) of 76.5% and 78.6%, and PASI 90, 50% and 55.5%, respectively. By week 264, safety rates did not increase and event rates were generally comparable between dose groups and between patients with and without dose adjustments. Treatment with ustekinumab for up to 5 years was safe and effective. The improved response was generally demonstrated after dose adjustments[27](A).

Studies have involved 766 patients over 18 years of age, diagnosed with plaque psoriasis for more than 6 months, candidates for phototherapy or systemic therapy, with initial PASI greater than 12, or compromise of more than 10% of body surface area. Group 1 with 255 patients on ustekinumab (UST) 45mg at weeks 0, 4 and 12, group 2 with 256 patients on UST 90mg at weeks 0, 4 and 12 and group 3 with 255 patients on placebo at weeks 0 and 4, and that from week 12 onwards they were randomized to receive 45 or 90mg of UST (crossover study). There was a significant improvement in the use of UST over placebo for the response of PASI 75 above and for PGA scores 0 or 1 at the 12th week of evaluation. Regarding the DLQI score, there was a significant increase in patients who reached a score of 0 or 1 compared to placebo (47.2% for the use of 45mg, NNT=2 and 46.4% for the use of 90mg of UST, NNT=2, p<0.001) in the 12th week, in addition to significant clinical improvement (increase of at least 5 points) in the SF-36 physical score (7.5% for 45mg NNT=14, 18.1% for 90mg NNT=6, p<0.001) and in the SF-36 mental score (10.7% for 45mg, NNT=10, 16.5% for 90mg, NNT=6, p<0.001)[28-31](A).

TABLE 3. EVALUATION OF ADALIMUMAB EXPRESSED BY THE ESTIMATED BENEFIT BY PERCENTAGE.

Author	Dose	Follow-up time	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)	PGA (%)
Cai L[17]	40mg + 80mg	12 weeks	77.8			80.5
Reich K[18-20]	80mg + 40mg	16 weeks	79.6		16.7	
Revicki D[21-23]	80mg + 40mg	16 weeks	64	43	19	
Asashina A[24]	40mg every 2 weeks	16 weeks	57.9			
Asashina A[24]	80mg every 2 weeks + 40mg from week 2	16 weeks	62.8			
Asashina A[24]	80mg every 2 weeks	16 weeks	81			
Gordon KB[26]	80mg + 40mg from week 1	12 weeks	49			
Gordon KB[26]	80mg + 40mg from week 2	12 weeks	76			

Other studies (N=1230) also randomized patients to: group 1 with 409 patients using UST 45mg at weeks 0, 4 and 12, group 2 with 411 patients using UST 90mg at weeks 0, 4 and 12 and group 3 with 410 patients on placebo at weeks 0 and 4, and who were randomized to receive 45 or 90 mg of UST from week 12 (crossover study). In the evaluation of the PASI, there was a significant improvement evaluated by obtaining the PASI 50, PASI 75, PASI 90 and PASI 100 responses for the use of UST 45mg (73%, NNT=2, 63%, NNT=2, 41.6% NNT=3 and 18.1%, NNT=6, respectively), and for the use of UST 90 mg (78.6%, NNT=2, 72%, NNT=2, 50.2%, NNT=2, 18.2% NNT=6). There was also a significant improvement in the use of UST compared to placebo in the visual analogue productivity scale at week 12 of evaluation (improvement of 72.6% for use of 45mg and of 71.4% for use of 90 mg of UST, p<0.001). As for the DLQI score, there was also a significant improvement in the use of UST compared to placebo (-9.13 vs. -0.53, respectively, p<0.001), with a difference of 48.9% for the use of UST 45mg (NNT=2, p<0.001) and 54.6% (NNT=2, p<0.001)[32-35]**(A)**.

Among 158 patients over 20 years of age, with moderate to severe plaque psoriasis diagnosed in the last 6 months, with at least 10% of body surface involvement or PASI of 12 or more, and eligible for phototherapy or systemic therapy, were randomized into 3 groups. Group 1 with 64 patients on UST 45mg, group 2 with 62 patients on UST 90mg per week and group 3 with 32 patients on placebo at weeks 0 and 4, followed by crossover at week 12. There was significant improvement assessed through the obtaining of PASI 50, PASI 75, PASI 90 responses for patients that used UST both at 45mg (69.9%, NNT=2, 52.9%, NNT=2, 29.6%, NNT=4, respectively, p<0.0001> and 90mg (71%, NNT=2, 61.2%, NNT=2, 40.3%, NNT=3, respectively, p <0.0001). Patients treated with 45mg and 90mg of UST also showed a significant improvement in mean DLQI scores (7.7 and 7.1, respectively, p <0.001), with improvement of 58.1% to 45mg (NNT=2, p<0.0001) and 54.1% to 90mg (NNT=2, p<0.0006)[36,37]**(A)**.

In one study, 61 patients received UST 45mg per week, compared to 60 patients on placebo. At week 12, the proportion of patients who achieved PASI 75 response was 62.2% higher in the group that received UST 45mg per week (NNT=2, p<0.001); with the PGA (percentage of patients who achieved PGA 0 or 1), there was a difference of 62.2% for patients using UST (NNT=2, p<0.001); and the mean improvement in quality of life for the DLQI score was -11 (p<0.001) also for the benefit of UST use[38]**(A)**.

A randomized, non-double-blind study comparing doses of 45 and 90 mg of ustekinumab with etanercept with a primary outcome measured by PASI 75 improvement at week 12 observed responses of 67.5%, 75.8% and 56.8%, respectively (P=0.01 in the comparison between ustekinumab 45mg / ethanercept and P<0.001 in the comparison between 90mg with etanercept). In the PGA 0/1 outcome, the results were 65.1%, 70.6% and 49.0% respectively (P<0.001 for both comparisons)[39]**(A)**.

RECOMMENDATIONS

Studies evaluating the efficacy and safety of ustekinumab for moderate to severe plaque psoriasis show improvement assessed by the PASI75 response (52.9-76.5% for 45mg and 61.2-78.6% for 90mg) and in quality of life according to the DLQI score (46.4-58.1%), as well as mild to moderate adverse events,

TABLE 4. EVALUATION OF USTEKINUMAB EXPRESSED BY THE ESTIMATED BENEFIT BY PERCENTAGE

Author	Dose	Follow-up Time	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PSI 100 (%)	PGA (%)	DLQI (%)
Langley RG[27]	45mg	244 weeks		76.5	50			
Langley RG[27]	90mg	244 weeks		78.6	55.5			
Kimball AB[28-31]	45mg	12 weeks						47.2
Kimball AB[28-31]	90mg	12 weeks						46.4
Reich K [32-35]	45mg	12 weeks	73	63	41.6	18.1	72.6	48.9
Reich K [32-35]	90mg	12 weeks	78.7	72	50.2	18.2	71.4	54.6
Nakagawa H [36,37]	45mg	12 weeks	69.9	52.9	29.6			58.1
Nakagawa H [36,37]	90mg	12 weeks	71	61.2	40.3			54.1
Tsai TF[38]	45mg	12 weeks		62.2			62.2	

in a 12-week period. Ustekinumab at doses of 45 and 90mg was superior to etanercept when evaluating PASI 75 and PGA 0/1 at 12 weeks of follow-up. After this period, although studies have carried out crossover, treatment with ustekinumab for up to five years was safe and effective following dose adjustment. (table 4)

What is the efficiency and what is the risk of guselkumab in the treatment of psoriasis?

Phase 3, randomized, double blind, placebo-controlled study. The study included a placebo-controlled period (weeks 0-16), a placebo-crossover and active treatment period (weeks 16-52) and a long-term extension phase. Eligible patients were randomized (1: 1: 1) for guselkumab 50 mg, 100 mg or placebo, injected subcutaneously at weeks 0, 4 and every 8 weeks thereafter. Patients receiving placebo were crossed to receive (1: 1) guselkumab 50 mg or 100 mg at weeks 16 and 20 and every 8 weeks. At week 16, a significantly greater proportion (P<0.001) of patients receiving guselkumab 50 mg (NNT=2) and 100 mg (NNT=2) versus placebo achieved IGA 0/1 (92.3% and 88.9% vs. 7.8%) and PASI90 (70.8% and 69.8% vs. 0%). Patients in the 50 mg and 100 mg groups of guselkumab and in the placebo group had improvement evaluated by the PASI75 response (89.2% and 84.1% vs 6.3%, P<0.001) at week 16; improvement was maintained until week 52. Incidences of treatment-emergent adverse events were comparable between groups up to week 16; the most commonly reported was nasopharyngitis[40]**(A)**.

The patients (n=992) were randomized (guselkumab: n=248; placebo: n=496; adalimumab: n=248) to 100 mg guselkumab at weeks 0, 4, 12 and 20; placebo at weeks 0, 4, 12 followed by guselkumab 100 mg at weeks 16, 20; or adalimumab 80 mg at week 0, 40 mg every 2 weeks, from week 1 to week 24. Guselkumab was superior to adalimumab at week 16 and 24 (P <0.001). From weeks 28 to 48, a better persistence of response was observed in maintenance groups with guselkumab versus abstinence groups (P<0.001). Of the non-responders of adalimumab who switched to guselkumab, 66.1% achieved PASI 90 at week 48. Guselkumab improved the outcomes reported by the patient. Adverse events were comparable between groups[41]**(A)**.

In one study the patients were randomized to 100 mg guselkumab (weeks 0 and 4, then every 8 weeks, n = 329); placebo → guselkumab (weeks 0, 4 and 12, then guselkumab at weeks 16 and 20, then every 8 weeks, n = 174); or adalimumab (80 mg weekly, 0.40 mg week 1, then 40 mg every 2 weeks to week 47, n = 334). Guselkumab was superior (P <0.001) to placebo at week 16 evaluated by IGA response 0/1, 85.1% vs 6.9% (NNT = 2) and 73.3% vs 2.9% as assessed by the PASI 90 response (NNT = 2). Guselkumab was also superior to adalimumab in IGA 0/1 (NNT = 6, P <0.001) and PASI 90 (NNT = 5, P <0.001) at week 16 85.1% vs 65.9% and 73.3% vs 49.7%); at week 24, 84.2% vs 61.7% (NNT = 5, P <0.001) and 80.2% vs 53.0% (NNT = 4, P <0.001)) and at week 48, 80.5 % vs 55.4% (NNT = 4, P <0.001) and 76.3% vs 47.9% (NNT = 4, P <0.001). In addition, guselkumab significantly improved outcomes reported by patients up to week 48. Rates of adverse events were comparable among treatments[42]**(A)**.

RECOMMENDATIONS

Studies evaluating the efficacy and safety of guselkumab for moderate to severe plaque psoriasis show improvement evaluated by the PASI90 response (50mg of 70.8% and 100mg of 69.8-73.3%) and IGA (0/1). Occurrence of mild to moderate adverse events, under analysis for a period of 36 weeks (table 5). Guselkumab (100mg) was superior to adalimumab (80 and 40mg) in IGA and PASI 90 response.

What is the effectiveness and what is the risk of ixekizumab in the treatment of psoriasis?

Randomized patients 2: 2: 2: 1 (n = 1346, UNCOVER-3), groups that received subcutaneous injections of 80 mg of ixekizumab every 2 weeks or every 4 weeks after an initial dose of 160 mg of ixekizumab, 50 mg of etanercept twice weekly or placebo, respectively, over a 12-week induction dosing period (weeks

TABLE 5. GUSELKUMAB ASSESSMENT EXPRESSED BY THE ESTIMATED BENEFIT BY THE PERCENTAGE

Author	Dose	Follow-up Time	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PGA (%)	DLQI (%)
Ohtsuki M [40]	50mg	16 weeks		89.2	70.8	92.3	
Ohtsuki M [40]	100mg	16 weeks		84.1	69.8	88.9	
Blauvelt A M[42]	100mg	16 weeks			73.3	85.1	

0 to 12). At week 12, patients entered the long-term follow-up (LTE) period, during which they received ixekizumab 80 mg every 4 weeks. After week 60, patients could increase their dose from 80 mg every 4 weeks to 80 mg every 2 weeks of ixekizumab until the end of study at the discretion of the investigator. The high response rates observed during the previous treatment periods persisted for 108 weeks of treatment. In patients receiving the 80 mg dose of ixekizumab every 2 weeks during induction and every 4 weeks during LTE (N = 385), the response rates observed were 93.4% for PASI 75; 79.7% for PASI 90; 56.3% for PASI 100; 82.6% for sPGA (0.1); and 57.0% for sPGA (0). Response rates were similar for each treatment arm at 108 weeks. At week 156 the observed response rate was 97.2% for PASI 75[44]. The frequency, severity, and distribution of treatment-emergent adverse events (TEAEs) were similar between treatment arms. The most frequently observed TEAEs (> 5%) during the LTE period included nasopharyngitis, upper respiratory tract infections, injection site reactions, arthralgia bronchitis, and headache. Of 1077 (84.5%) TEAEs reported during the LTE period, 910 (85%) were of mild or moderate severity. Of the TEAEs of special interest that occurred during LTE, Candida infections were the most common, occurring at a rate of 3.8%. Overall, the results presented demonstrate that ixekizumab is well tolerated and provides a long-term and persistent clinical response[43,44]**(A)**.

In UNCOVER-1, patients were randomized 1: 1: 1 to receive subcutaneous ixekizumab 80 mg every 2 weeks (IXE2S), ixekizumab 80 mg every 4 weeks (IXE4S) (each with a starting dose of 160 mg) or placebo (PBO) for 12 weeks. In UNCOVER-2, patients were randomized 2: 2: 2: 1 to receive IXE2S, IXE4S (each with an initial dose of 160 mg), etanercept 50 mg twice weekly or placebo by 12 weeks. In both trials, the 12-week induction period was followed by a 48-week (12-60) randomized maintenance period, in which those responding to ixekizumab at week 12 (sPGA = 0 or 1) were randomized (1 : 1: 1) to receive subcutaneous placebo, IXE4S. A total of 1226 treated patients reached the sPGA 0, 1 at week 12 and entered the maintenance phase; of these patients, 402 and 416 were randomized to PBO and IXE4S, respectively. Among patients who discontinued treatment, 157 (82.2%) of IXE4S / PBO and 176 (83.4%) of IXE2S / PBO they had an sPGA of ≥3 at week 60; the mean time to relapse was approximately 20 weeks regardless of the induction dose. At week 60, continuously treated patients maintained high levels of PASI and sPGA responses (90.0% PASI 75 IXE2S / IXE4S, 81.9% sPGA 0.1, IXE2S / IXE4S, non-responder imputation). After 24 weeks of retreatment with IXE4S (IXE2S / PBO / IXE4S and IXE4S / PBO / IXE4S), 87% (107 of 123) and 95% (97 of 102) (observed), respectively, of patients recovered PASI 75 and 70.7% (104 of 147), and 82.3% (107 of 130) (observed) recovered aPGA 0, 1. In general, adverse events in continuously treated and portrayed patients were comparable[45,46,47]**(A)**.

In a study (UNCOVER-2) that evaluated 347 patients on ixekizumab every 4 weeks, 351 patients on ixekizumab every 2 weeks, 358 patients on etanercept and 168 patients on placebo, an improvement was observed for PASI 75 in the first 12 weeks of 77.5%, 89.7%, 41.6% and 2.4% respectively (P <0.0001 for comparisons between ixekizumab/placebo and ixekizumab/etanercept). Regarding the PASI 90 improvement, the results were 59.7%, 70.7%, 18.7% and 0.6% respectively (P <0.0001 for the comparisons between ixekizumab/placebo and ixekizumab/etanercept). When analyzing PASI 100 improved, it was observed 30.8%, 40.5%, 5.3% and 0.6%, respectively, P <0.0001 for the comparisons between ixekizumab/placebo and p <0.0082 between ixekizumab/etanercept). Similar results were observed in the PGA 0/1 outcome[47]**(A)**.

Study (UNCOVER 3) evaluating 386 patients on ixekizumab every 4 weeks, 385 patients on ixekizumab every 2 weeks, 382 patients on etanercept and 193 patients on placebo, found improvement in PASI 75 in the first 12 weeks of 84.2%, 87.3%, 53.4% and 7.3% respectively (P <0.0001 for the comparisons between ixekizumab/placebo and ixekizumab/etanercept). Regarding PASI 90 improvement, the results were 65.3%, 68.1%, 25.7% and 3.1%, respectively. When analyzing PASI 100 improved, it was observed 35%, 37.7%, 7.3% and 0% respectively (P <0.0001 for all comparisons between ixekizumab/placebo and between ixekizumab/etanercept). Also in this study, similar results were observed in the PGA 0/1 outcome[47]**(A)**.

The 12 patients in this study were randomized 1: 1 to receive 80 mg of ixekizumab every two (IXE2S) or four (IXE4S) weeks during the induction period (0-12 weeks) after an initial dose of 160 mg ixekizumab. All patients received 80 mg ixekizumab (IXE4S) during the maintenance period (12-48 weeks) with the final dose of ixekizumab administered at week 44. The mean time to an improvement of at least 1 point or

2 points in the baseline of the PatGA score was 5.0 and 10.0 days for patients randomized to IXE2S and 6.0 and 13.5 days for patients randomized to IXE4S. All patients achieved at least a 50% or 75% improvement in PASI since the beginning of weeks 2 and 4, respectively. At least half of the patients achieved a 4-point improvement over baseline Itch NRS on Day 14. Improvement in disease was conspicuously evident within one week of treatment in patient photographs[48]**(A)**.

RECOMMENDATIONS

Studies in the evaluation of the efficacy and safety of Ixekizumab and moderate to severe plaque psoriasis show improvement in PASI 75 (90-93.4%), PASI 90 (79.7%), PASI 100 (56.3%), PatGA, Itch NRS and sPGA (57-81.9%). Results of ixekizumab used in doses every two to four weeks were significantly better for PASI75, 90, 100 and IGA 0/1 outcomes compared to etanercept. Occurrence of mild to moderate adverse events in a 96-week period. (table 6)

What is the efficacy and what is the risk of secukinumab in the treatment of psoriasis?

Treatment with subcutaneous 300 or 150 mg secukinumab in a FI or RAN regimen. FI was administered once every 4 weeks, and in the RAN regimen, participants received placebo until the onset of relapse, defined as ≥20% loss of maximal PASI improvement versus baseline plus loss of PASI 75 response. When the relapse onset criterion was met, the subject received active secukinumab at the originally randomized dose (every 4 weeks) until the PASI 75 response was restored, at which point the subject started receiving placebo again. A group of 168 subjects received secukinumab 300 mg IF and another group with 172 received secukinumab 300 mg RAN. Secukinumab 300 mg IF maintained high efficacy: at the end of year 3, the PASI 90 response was 63.8% and PASI 100 was 42.6%. The mean absolute PASI remained low (2-4) from week 52 to week 152 with 300 mg FI, with approximately two-thirds of individuals reporting no impact of the skin disease on their lives (Dermatology Quality of Life Index of 0/1). Improvements in overall scores and subscales in all quality of life instruments were well supported. The IF dosage was consistently more effective than the RAN. No new safety signal has been identified for year 3[49]**(A)**.

Patients ≥ 18 years, diagnosis (with ≥6 months) of moderate to severe plaque psoriasis (PASI) ≥12; IGA of 3 or 4; BSA ≥10% were selected for a study that had a 12-week induction period, a 40-week maintenance period, and an 8-week follow-up period. Patients in the ERASURE trial were randomly assigned in a 1: 1: 1 ratio to receive secukinumab at a dose of 300 mg, secukinumab at a dose of 150 mg or placebo; those in the FIXTURE study were randomly assigned 1: 1: 1: 1 to receive secukinumab at the 300 mg or 150 mg dose, etanercept or placebo. Patients randomly assigned to secukinumab in both studies received two subcutaneous injections of 150 mg secukinumab (there is, 300 mg total) or one 150 mg injection plus one placebo injection, with both injections administered once weekly in the beginning and at weeks 1, 2, 3 and 4 and then every 4 weeks until week 48. Patients randomly assigned to etanercept received 50 mg given subcutaneously twice weekly from baseline to week 12 and then once weekly until week 51, according to the standard dosing regimen. In the FIXTURE study, the placebo group received placebo injections corresponding to the secukinumab and etanercept regimens, and the secukinumab and etanercept groups received placebo injections corresponding to the other active drug regimen, in order to maintain a dual simulation design. In the ERASURE study, patients randomly assigned to receive placebo received placebo injections corresponding to the secukinumab regimens. In each study, patients in the placebo group who did not meet the criteria for a 75% or greater reduction in baseline PASI score (PASI 75) at week 12 were again randomized at 1: 1 ratio to receive secukinumab at a dose of 300 mg or 150 mg; those who achieved the PASI 75 response at week 12 continued to receive placebo. The proportion of patients meeting the criteria for PASI 75 at week 12

TABLE 6. EVALUATION OF IXEKIZUMAB EXPRESSED BY THE ESTIMATED BENEFIT BY MEANS OF THE PERCENTAGE.

Author	Dose	Follow-up Time	PASI 50 (%)	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)	PGA (%)
Blauvelt A [43,44]	80mg every 4 weeks	12 weeks		93.4	79.7	56.3	57.0
Blauvelt A [43,44]	80mg every 2 weeks	60 weeks		90			81.9

was higher in the use of secukinumab compared to placebo or etanercept: in the ERASURE study, rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, rates were 77.1% with 300 mg of secukinumab, 67.0% with secukinumab 150 mg, 44.0% with etanercept and 4.9% with placebo (P <0.001)[50]**(A)**.

The proportion of patients with a response of 0 or 1 in the global evaluation of the investigator modified at week 12 was higher with secukinumab than with placebo or etanercept: in the ERASURE study, rates were 65.3% with 300 mg of secukinumab, 51.2% with 150 mg of secukinumab and 2.4% with placebo; in the FIXTURE study, rates were 62.5% with 300 mg of secukinumab, 51.1% with 150 mg of secukinumab, 27.2% with etanercept and 2.8% with placebo (P <0.001). Rates of infection were higher with secukinumab than with placebo in both studies and were similar to those of etanercept[50]**(A)**.

RECOMMENDATIONS

Studies in the evaluation of the efficacy and safety of secukinumab for moderate to severe plaque psoriasis show improvement assessed by the PASI 75 response (77.1-81.6% for 300mg and 67.0-71.6% for 150mg) and IGA 0 or 1, and maintenance of quality of life (DLQI) with use for up to 3 years. Occurrence of mild to moderate adverse events. The best results were obtained with weekly dosing of 300 mg in the first 4 weeks of treatment and then a dose of 300 mg of secukinumab every 4 weeks (table 7).

The proportion of patients who fulfilled the criteria for PASI 75 at week 12 was higher in the use of secukinumab (300mg - 77.1%, 150mg - 67%) compared to placebo (4.9%) or etanercept (50mg 2x/44%), as well as the proportion of patients with a response of 0 or 1 in the overall evaluation of the investigator modified at week 12 was higher with secukinumab (300mg - 62.5%, 150mg - 51.1%) than placebo (2.8%) or etanercept (27.2%). PASI 90 and PASI 100 responses at week 12 were also significantly higher in the group that used secukinumab 300mg compared to the group that used etanercept (54.2% vs.20.7% and 24.1% vs. 4.3%, respectively).

Is there a safety and effective difference between immunobiological treatments?

Adults between 18 and 75 years of age with moderate to severe stable plaque psoriasis (> 6 months) PASI ≥ 12, sPGA ≥ 3 and BSA ≥10 were included in the study, and each study included an induction phase of 12 weeks and a maintenance phase of 40 weeks. Patients were randomly assigned in a ratio of 2: 2: 1: 1 to receive brodalumab at the dose of 210 mg or at the dose of 140 mg (subcutaneous injection on day 1 and weeks 1, 2, 4, 6, 8 and 10), ustekinumab or placebo. At week 12, patients who were originally randomized to receive brodalumab underwent repeated randomization at a ratio of 2: 2: 2: 1 to one of four maintenance regimens: brodalumab at 210 mg every two weeks, 140 mg every two weeks, 140 mg every 4 weeks or 140 mg every 8 weeks, stratified according to body weight (≤100 kg or >100 kg), induction and response regimen and week 12 (sPGA score, 0 or ≥ 1) response. Patients who were originally randomly assigned to receive placebo were transferred to brodalumab at the dose of 210 mg every two weeks. Patients who were originally randomized to receive ustekinumab continued to receive ustekinumab every 12 weeks to week 52, while patients who were still receiving the regimen could receive brodalumab at the 210 mg dose every two weeks in an open-label extension study. Blinding of the original treatment was maintained during the re-randomization process and up to week 52. At week 12, PASI 75 response rates were higher with brodalumab at the 210 mg and 140 mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively,

TABLE 7. EVALUATION OF SECUKINUMAB EXPRESSED BY THE ESTIMATED BENEFIT BY PERCENTAGE.

Author	Dose	Follow-up Time	PASI 75 (%)	PASI 90 (%)	PASI 100 (%)
Bissonnette R [49]	300mg/ 150mg	3 years		63.8	42.6
Langley RG [50]	300mg	12 weeks	81.6		
Langley RG [50]	150mg	12 weeks	71.6		
Langley RG [50]	300mg	12 weeks	77.1		
Langley RG [50]	150mg	12 weeks	67.0		

vs. 6% [AMAGINE-3], NNT = 2, P <0.001); the rates of 0 to 1 sPGA scores were also higher with brodalumab (P <0.001). At week 12, PASI response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs 19% [AMAGINE-3], (NNT = 5 and NNT = 6, P <0.001). The rates of PASI 100 response with 140 mg of brodalumab were 26% in AMAGINE-2 (P = 0.08 for the comparison with ustekinumab) and 27% for AMAGINE-3 (P = 0.007). Mild or moderate infections with candida more frequent with brodalumab than with ustekinumab or placebo. Up to week 52, severe infectious episode rates were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumabe[51-53]**(A)**.

In another study with a similar population, patients were randomized 3: 3: 1: 3 (CZP 400 mg every 2 weeks or CZP 200 mg every 2 weeks (after loading doses of 400 mg at weeks 0, 2 and 4) for 16 weeks, placebo every 2 weeks for 16 weeks, or etanercept 50 mg twice weekly for 12 weeks. Double-blind treatments with CZP and placebo were administered subcutaneously, treatment with etanercept was given subcutaneously. At week 16, patients in the CZP treatment groups who achieved a PASI were randomized (2: 2: 1): from CZP 400 mg every 2 weeks to CZP 200 mg every 2 weeks, and from CZP 200 mg every 2 weeks or placebo, and from CZP 200 mg every 2 weeks to CZP 400 mg every 4 weeks, CZP 200 mg every 2 weeks, or placebo for the maintenance period of 32 weeks. PASI 75 placebo-treated responders continued on placebo during the maintenance period and etanercept-treated PASI 75 responders were randomized (2: 1) to 200 mg CZP every 2 weeks (after 400 mg loading doses at weeks 16, 18 and 20) or placebo. PASI 75 non-responders at week 16 entered an escape arm and received treatment with CZP 400 mg every 2 weeks. At week 12, the PASI 75 response rate was significantly higher for patients treated with CZP versus patients treated with placebo (NNT = 2, P <0.0001). The differences were evident between the drug and placebo groups as early as week 4 and increased up to week 16. At week 12, CZP 400 mg was higher and CZP 200 mg (NNT = 19, P <.0001) and it was not lower than etanercept for the PASI 75 response rate. Similar trends occurred for the PGA 0/1 and PASI 90 response rates for both CZP versus placebo doses[54]**(A)**.

In another study involving the Investigator Global Assessment (IGA) ≥ 3, ≥ 10% of the body surface area, patients were randomized to 100 mg guselkumab (weeks 0 and 4, then every 8 weeks; n = 329); placebo → guselkumab (weeks 0, 4 and 12, then guselkumab at weeks 16 and 20, then every 8 weeks, n = 174); or adalimumab (80 mg weekly, 0.40 mg week 1, then 40 mg every 2 weeks to week 47, n = 334). Guselkumab was superior (P <0.001) to placebo at week 16, 85.1% vs 6.9% at IGA from 0/1 (NNT = 2) and 73.3% vs 2.9% at PASI 90 (NNT = 2). Guselkumab was also superior to adalimumab in IGA 0/1 (NNT = 6, P <0.001) and PASI 90 (NNT = 5, P <0.001) at the 16th week 85.1% vs 65.9% and 73.3% vs 49.7%); at week 24, 84.2% vs 61.7% (NNT = 5, P <0.001) and 80.2% vs 53.0% (NNT = 4, P <0.001)) and at week 48, 80.5% vs 55.4% (NNT = 4, P <0.001) and 76.3% vs 47.9% (NNT = 4, P <0.001). In addition, guselkumab significantly improved patient outcomes by week 48. Adverse event rates were comparable among treatments[42]**(A)**.

Nine hundred and three patients over 18 years of age with a diagnosis of moderate to severe plaque psoriasis for more than six months, who are candidates for phototherapy or systemic treatment, with a PASI score of 12 or greater, with a minimum PGA of 3, on a scale of 0 to 5, with involvement of at least 10% of the body surface were included in the study. Patients were allocated to 3 groups: group 1 with 347 patients taking ethanercept 50mg, twice weekly, group 2 with 209 patients on ustekinumab (UST) 45mg at weeks 0 and 4, and group 3 with 347 patients using ustekinumab 90mg at weeks 0 and 4. There was a significant improvement to PASI 75 for the use of UST 45mg in relation to etanercept in 10.7% (95% CI 2.4 to 19, p = 0.001, NNT = 10) and for the use of UST 90mg in relation to etanercept in 17% (95% CI 10 to 24, p <0.001, NNT = 6). For PASI 90 the benefit was 13.3% for UST 45mg in relation to etanercept (95% CI 5.8 to 20.7, p <0.001, NNT = 8) and 21.6% for use of UST 90mg in with etanercept (95% CI 14.6 to 28.5, p <0.001, NNT = 5). In the evaluation of the PGA score regarding lightening of the lesions, the benefit was 16.1% for UST 45mg compared to etanercept (IC95% 7.6 to 24.2, p <0.001, NNT = 7) and 21.6% for the use of UST 90mg in relation to etanercept (95% CI 14.4 to 28.6, p <0.001, NNT = 5). Adverse events were reported in 70% of the patients receiving ethanercept, 66% of patients taking UST 45mg and 69.2% of patients using UST 90mg[39]**(A)**.

Authors studied the intervention group with 139 patients taking 200mg of briakinumab at weeks 0 and 4 and 100mg at week 8, 139 patients taking 50mg of etanercept, twice a week for 11 weeks, and

72 patients on placebo. In the evaluation by PGA, the benefit was 42.7% for briakinumab compared to etanercept (p <0.001, NNT = 3) and 68.5% for briakinumab compared to placebo (p <0.001, NNT = 2). For PASI above 75 the response at 12 weeks was 41% for briakinumab in relation to etanercept (p <0.001, NNT = 3) and 73.7% in relation to placebo (p <0.001, NNT = 2). Serious adverse events were reported in 1.4% of patients in the briakinumab group, 0.7% in the etanercept group, and 2.8% in the placebo group[2]**(A)**.

In the lack of "head to head" trials comparing all the different immunobiological drugs in the treatment of moderate to severe plaque psoriasis, to assess and compare the different biological treatments, tables 1, 2, 3 and 4 of each drug separately and table 5 with all drugs, and the benefit estimated value by the necessary number to treat (NNT) to achieve PASI 50, PASI 75 and PASI 90, in addition to the analysis of lightening by the PGA and the DLQI score, despite of the possibility of comparing the NNTs of the different studies.

RECOMMENDATIONS

In the evaluation of immunobiological drugs in relation to the PASI 75 score, similar benefits were found in: Etanercept, Infliximab, Adalimumab, Ustekinumab, Guselkumab, Ixekizumab, Secukinumab.

Guselkumab was superior to adalimumab in IGA 0/1 and PASI 90.

There was a significant improvement for PASI 75 and in the PGA score assessment for the use of ustekinumab in relation to etanercept.

Results of ixekizumab used in doses every two to four weeks were significantly better for PASI75, 90 100 and IGA 0/1 outcomes compared to etanercept.

There was a significant improvement for PASI 75, 90 and 100, as well as for PGA0/1 for use of secukinumab in relation to etanercept

Although not all drugs have studies regarding the PGA score the best results were with: Ustekinumab, Guselkumab, Secukinumab and Ixekizumab.

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