Expert recommendations for biological treatment in patients with psoriasis

Nancy Podoswa-Ozerkovsky,^{1*} Mario Amaya-Guerra,² José F. Barba-Gómez,³ Lorena Estrada-Aguilar,⁴ Minerva Gómez-Flores,⁵ Adriana L. Lopez-tello-Santillan,⁶ César A. Maldonado-García,⁷ Mónica I. Rivera-Gómez,⁸ Delfina G. Villanueva-Quintero⁹ and Gladys León-Dorantes¹⁰

¹Dermatology Department, Regional General Hospital No. 1, Instituto Mexicano del Seguro Social, Mexico City; ²Dermatology Department, Health and Development Center, Universidad de Monterrey, Nuevo León; ³Instituto Dermatológico de Jalisco Dr. José Barba Rubio, Jalisco; ⁴Dermatology Department, Hospital Regional "Lic. Adolfo López Mateos", Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City; ⁵Dermatology Department, University Hospital, Universidad Autónoma de Nuevo León, Nuevo León; ⁶Dermatology Department, Instituto de Seguridad Social del Estado de México y Municipios, State of Mexico; ⁷Psoriasis Clinic Head Office, Centro Dermatológico "Dr. Ladislao de la Pascua", Mexico City; ⁸Dermatology Department, Specialty Hospital, Centro Médico Nacional La Raza, Instituto Mexicano del Seguro Social, Mexico City; ⁹Clinical Research, Centro de Atención en Enfermedades Inflamatorias, Jalisco; ¹⁰Unidad de Innovación Clínica y Epidemiológica del Estado de Guerrero, Guerrero. Mexico

Abstract

In recent years, the introduction of a series of biological drugs for the treatment of psoriasis has considerably increased the therapeutic armamentarium of doctors, and thus a strongly positive impact on the control of this condition has been achieved. With the purpose to provide the best recommendations for the use of these biological agents in patients with psoriasis, the Mexican group of psoriasis experts, PSOMEX, has developed recommendations in order to improve the understanding and therapeutic positioning of this type of medications.

KEY WORDS: Psoriasis. Psoriatic arthritis. Recommendations. Biological agents. Mexico.

Recomendaciones de expertos para el tratamiento biológico en pacientes con psoriasis

Resumen

En los últimos años, la introducción de diversos medicamentos biológicos para el tratamiento de la psoriasis ha aumentado considerablemente el arsenal terapéutico del médico, con lo cual se ha logrado un fuerte impacto positivo en el control de la enfermedad. Con el fin de proveer de las mejores recomendaciones para el uso de estos biológicos en los pacientes afectados de psoriasis, el grupo mexicano de expertos en psoriasis PSOMEX ha formulado recomendaciones para mejorar la comprensión y el posicionamiento terapéutico de este tipo de medicamentos.

PALABRAS CLAVE: Psoriasis. Artritis psoriásica. Recomendaciones. Agentes biológicos. México.

Introduction

Psoriasis is a chronic skin condition with a highly complex immune-mediated inflammatory basis. It is a common entity, with estimated prevalence rates between

1 and 4 % in the world population and is associated with multiple comorbidities, significant deterioration of quality of life and social and economic functioning, as well as a reduction in life expectancy¹.

In the last two decades, and as a result of the elucidation of several pathophysiological mechanisms

Correspondence:

*Nancy Podoswa-Ozerkovsky

E-mail: npodoswa@yahoo.com.mx

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involved in the development of the disease, various biologic therapeutic agents have emerged, which have become the cornerstone in the treatment of patients with psoriasis. By 2013, approximately 25 % of patients with moderate to severe psoriasis in the world were already being treated with biological drugs^{2,3}.

Objectives of the recommendations

In order to develop practical recommendations that allow keeping the dermatologist updated in the field of optimal management of biological drugs, the group of experts of the Mexican group for the study of psoriasis and immune-mediated diseases (PSO-MEX) gathered to develop said recommendations, which are based on the best available evidence, as well as on clinical experience of the group members.

Method

Multiple relevant questions concerning psoriasis biological treatment were defined. An extensive literature search was conducted in PubMed/Medline to identify case reports, case series, review articles, and clinical trials using the terms, “psoriasis” and “biologics”. The review was limited to articles published in English and Spanish. The answers were formulated according to evidences found in said review and, in addition, included the experts individual experience. According to the Delphi method, voting was carried out to achieve a level of agreement regarding the answers, with consensus being defined when 70 % of participants reached an agreement on the recommendation.

Recommendations

1. What is a biological drug and which ones are available?

The term “biological drug” refers to monoclonal antibodies and fusion proteins designed to selectively block biological molecules (cytokines, enzymes etc.).

Currently, the biological drugs available for the treatment of psoriasis and psoriatic arthritis are anti-TNF agents (infliximab, etanercept, adalimumab, certolizumab pegol and golimumab), anti-IL12/anti-IL23 agents (ustekinumab), anti-IL17 agents (ixekizumab, secukinumab, and brodalumab) and anti-IL23 agents (guselkumab, tildrakizumab and risankizumab (Table 1)).⁴⁻¹⁰

Table 1. Biologic agents for the treatment of psoriasis

Biologic agent type	Drug
Anti-TNF	Infliximab, etanercept, adalimumab, certolizumab pegol, golimumab
Anti-IL12/anti IL23	Ustekinumab
Anti-IL17	Ixekizumab, secukinumab, brodalumab
Anti-IL23	Guselkumab, tildrakizumab, risankizumab

2. Who is candidate for a biological drug?

Patients with moderate to severe psoriasis in whom conventional systemic treatments have resulted in primary or secondary therapeutic failure or are contraindicated or not tolerated, are candidates for biological treatment,¹¹ as well as patients with moderate to severe psoriasis classified as “high-need”, where biological treatment can be indicated as first-line (Table 2).

3. Who indicates biological management?

Treatment should be indicated and supervised by dermatologists with experience in the diagnosis and treatment of psoriasis and with extensive knowledge on the management of biologic agents.

4. How to select the biologic agent?

The decision on which agent is appropriate to start with must be individualized, taking into consideration various factors (see pre-treatment evaluation).^{12,13}

5. Absolute contraindications:

- Hypersensitivity to the drug.
- Serious active infections.
- Family or personal history of demyelinating disease contraindicates the use of anti-TNF agents.
- New York Heart Association class III or IV severe heart failure contraindicates the use of anti-TNF agents.

In case of family or personal history of inflammatory bowel disease, avoiding the use of anti-IL17 agents is suggested.

6. Precautions for prescription

Anti-TNF drugs should be prescribed with caution in patients with the following conditions:

- History of recurrent infections or previous serious infection.
- History of hematological diseases.
- New York Heart Association class I and II heart failure.
- Personal or family history of lupus.
- Pregnancy and lactation potential (see corresponding section).

Table 2. Psoriasis severity categorization

Instrument	Severity			
	Mild	Moderate	Severe	High-need
PASI	0-5	5-10	> 10	– Involvement of high impact areas: face, hands, feet and genitals. – Presence of psoriatic arthropathy. – Rapid generalization – Resistance to treatments. – Severe forms, erythroderma, pustular forms.
BSA	< 3 %	3-8 %	> 10 %	
DLQI	2-5	6-10	11-20	21-30
PSSI (Psoriasis Scalp Severity Index)	< 50% of surface involved, mild or minimal erythema, infiltration and pruritus	< 50% of surface involved, moderate erythema, infiltration and pruritus	> 50% of surface involved, moderate or severe erythema, infiltration, and pruritus, or presence of scarring alopecia or involvement in visible areas of the face	

PASI 75 = 75 % reduction according to the Psoriasis Area and Severity Index, BSA = body surface area, DLQI = Dermatology Life Quality Index, PSSI = Psoriasis Scalp Severity Index.

7. Pretreatment evaluation

Before starting the patient on biologic agents, a patient baseline evaluation should be obtained with complete history and physical examination, with special attention to the psoriasis clinical form, previous treatments, present comorbidities (psoriatic arthritis and type of arthritis, history of neoplasms, chronic infections, lymphadenopathy, neurological, heart or autoimmune disease, etc.), preferences and availability for storage and application of the drug.

The patient should be broadly informed about the risks and benefits of the treatment, as well as the precautions to be taken during its administration.^{13,14}

8. Recommended laboratory and imaging tests

The following studies are recommended for all patients prior to the start of biological treatment:^{14,15}

- Complete blood count, complete metabolic panel including liver function tests, serology for human immunodeficiency virus, hepatitis B and C, pregnancy test, purified protein derivative skin test (for tuberculosis detection), interferon gamma-release test and chest X-ray.
- Immunology panel (anti-nuclear, anti-DNA antibodies), which, although not strictly necessary, is recommended if there is a family history of lupus or in patients who develop symptoms or signs suggestive of lupus during treatment. Positivity alone is nonspecific and does not preclude treatment to be initiated in a patient.

9. Vaccination

Updating the vaccination schedule should be tried prior to initiating biological treatment; live attenuated

virus or live virus vaccines should be avoided during biological treatment. The recommendation is no not vaccinate two weeks before starting treatment with biologic agents and waiting 6 months after discontinuing the biological to vaccinate (12 months for varicella zoster vaccine). Treatment can be reinitiated four weeks after vaccination. Inactivated virus vaccines can be applied during biological treatment, and applying influenza and pneumococcal vaccines during treatment is recommended. Live or live attenuated vaccines should neither be administered to newborns who have been exposed to biologic agents in utero; vaccination should be deferred for six months.¹⁶

10. Transition from systemic to biological or from biological to biological treatment

In the event of primary or secondary failure, transition can be carried out directly, even when overlapping with previous systemic or biological treatment. If the transition is required due to the development of an adverse event, starting the biological drug once the unwanted side effect has disappeared is recommended¹⁷⁻¹⁹.

11. Monitoring during biological treatment and response evaluation

During treatment, patients should be periodically evaluated to monitor treatment response, as well as possible development of complications. Patient assessment intervals are variable, but at least a quarterly evaluation is recommended.

Laboratory tests are recommended at intervals of three to six months or earlier, in case of exposure to

risks or development of signs or symptoms suggestive of adverse effects.²⁰⁻²²

12. *Biological treatment optimization: dose increase, modification of administration intervals, combinations*

In case of partial response or loss of effectiveness, first trying to optimize the treatment with the following strategies before switching to another biologic agent is always recommended:

- Increase the dose of the drug or shorten dosing intervals (Table 3).
- Combination with topical agents (topical steroids, vitamin D analogs, or keratolytic, reducer or retinoid agents), with phototherapy or with conventional systemic medications (methotrexate, cyclosporine for short periods).
- Eliminate or modify factors that contribute to loss of effectiveness: comorbidities, intercurrent infections, overweight, smoking, alcohol intake, and dietary factors.^{18,23-26}

Combination of two or more biologic agents is not recommended

13. *Drug exchange (switching)*

Switching the drug is recommended when there is either primary or secondary therapeutic failure that does not respond to upgrading or when a drug-related adverse event develops. If this is done due to therapeutic failure, waiting a period to restart with a different biologic agent is not necessary; the usual dosing schedule (induction and maintenance dose) should be used. If the switch is related to the development of an adverse event, waiting until the event has resolved to restart with another biologic agent will be necessary.

The switch can occur between drugs of the same therapeutic group if required due to therapeutic failure. If the switch is driven by the development of adverse events considered as “class” effects, switching to a drug with another mechanism of action is advised.²⁷

14. *Intermittent treatment vs. continuous treatment*

In general, with biologic agents, intermittent or rotational treatments are not recommended.

15. *When to discontinue biological therapy*

- Primary failure: inability to achieve at least a reduction of 50 % in the Psoriasis Area and Severity Index (PASI 50) in the time frames established for each drug.
- Secondary failure that does not respond to optimization strategies.
- Development of a serious adverse event.
- Elective major surgeries.

- Need for vaccination.
- Pregnancy (see corresponding section).

16. *Treatment restart after discontinuation*

Etanercept, adalimumab, ustekinumab, ixekizumab, secukinumab can be restarted with good response recapture.

Restarting with induction doses depends on the severity of the condition and the time elapsed since the last dose. It will be necessary considering it if more than three or four half-lives of the drug have elapsed since the last administration

It is not advisable to restart infliximab after prolonged interruptions (more than 12 weeks) due to a high risk of loss of effectiveness, as well as adverse reactions mediated by anti-drug antibodies.²⁸⁻³⁰

17. *Drug interactions*

Biological drugs can accelerate the metabolism of several drugs or increase their response; therefore, drug interactions should be monitored (Table 4).

Biologic agents in special populations and situations

1. *Pediatric age*

In children who are candidates for biological treatment, adalimumab can be used from four years of age on, etanercept from 6 years on and ustekinumab from 12 years on.³¹⁻³⁴

2. *Geriatric population (> 65 years)*

Biological treatment is effective and safe in this population. There could be an increased risk of adverse effects such as infection, neoplasm or drug interactions.³⁵

3. *Pregnancy, lactation, and reproductive potential*

Avoiding pregnancy during biological treatment is recommended.

There are no known interactions between biological treatments and contraceptive methods.

With pregnancy plans, discontinuing biologic agents for the following periods is recommended: etanercept, three weeks; infliximab, six weeks; adalimumab, six months; ustekinumab, 15 weeks.³⁶

Should biological treatment be required during pregnancy, anti-TNF agents would be the first choice and, among them, certolizumab pegol as first-line, followed by etanercept.³⁷

Discontinuing monoclonal antibodies in pregnant women at 16 weeks of gestation is recommended in order to avoid transplacental passage of antibodies.

Informing the pregnant patient on biological treatment about the “theoretical” risks of spontaneous

Table 3. Characteristics of different biological drugs

Drug	Indications	Mechanism of action	Half life	Administration route	Psoriasis induction dose	Psoriasis maintenance dose	PASI75 ATR	Psoriasis optimization
Etanercept	Rheumatoid arthritis, JIA, psoriatic arthritis, axial spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, psoriasis in adults, severe pediatric psoriasis from age 6 onwards	Anti-TNF α and Anti-TNF β	Approx. 70 hours	Subcutaneous	50 mg BIW (maximum 12 weeks) In children ≥ 2 years: 0.8 mg/kg/week (maximum 50 mg)	25 mg BIW or 50 mg/week	12 weeks	50 mg BIW
Infliximab	CD, ulcerative colitis, rheumatoid arthritis + methotrexate, ankylosing spondylitis, psoriatic arthritis, psoriasis	Anti-TNF α (Anti-IgG1)	7.7 to 9.5 days	Intravenous	5 mg/kg	5 mg/kg at 2 and 6 following weeks and subsequently every 8 weeks	14 weeks	Dose increase to up to 10 mg/kg. Interval reduction to down to 4 weeks
Adalimumab	JIA, hidradenitis suppurativa, CD, pediatric psoriasis, pediatric CD, pediatric uveitis	Anti-TNF α (anti-IgG1)	Approx. 2 weeks	Subcutaneous	Pediatric dose: According to weight: 15-30 kg, 20 mg; > 30 kg, 40 mg Normal dose: 80 mg/week on weeks 0 and 1 and then every 2 weeks	15-30 kg, 20 mg every 2 weeks > 30 kg, 40 mg every 2 weeks	16 weeks	40 mg/week
Certolizumab pegol	Rheumatoid arthritis + methotrexate, axial spondyloarthritis, psoriatic arthritis, psoriasis	Anti-TNF α	14 days	Subcutaneous	2 200-mg injections on weeks 0, 2 and 4	200 mg every 2 weeks	16 weeks	400 mg every 2 weeks if response is insufficient
Ustekinumab	Psoriasis, pediatric psoriasis, psoriatic arthritis	Anti-IL12/anti-IL23	3 weeks	Subcutaneous	45 mg + 45 mg at 4 weeks If > 100 kg, 90 mg + 90 mg at 4 weeks Children: < 60 kg, 0.75 mg/kg weeks 0 and 4; 60-100 kg, 45 mg weeks 0 and 4; > 100 kg, 90 mg weeks 0 and 4	45 mg/12 weeks; if > 100 kg, 90 mg/12 weeks Children: < 60 kg, 0.75 mg/kg week 12; 60-100 kg, 45 mg, week 12; > 100 kg, 90 mg week 12	28 weeks	From 45 mg to 90 mg, 90 every 8 weeks
Ixekizumab	Psoriasis, psoriatic arthritis	Anti-IL17A	13 days	Subcutaneous	160 mg week 0 + 80 mg weeks 2, 4, 6, 8, 10 and 12	80 mg every 4 weeks	16-20 weeks	
Secukinumab	Psoriasis	Anti-IL17A	27 days	Subcutaneous	300 mg weeks 0, 1, 2 and 3	300 mg/week (in two 150 mg injections)	16 weeks	300 mg/2 to 3 weeks
Guselkumab	Psoriasis	Anti-IL23	15-18 days	Subcutaneous	100 mg weeks 0 and 4	100 mg/8 weeks	16 weeks	

PASI 75 = 75 % reduction according to the Psoriasis Area and Severity Index, ATR = average time to response, JIA = juvenile idiopathic arthritis, CD: Crohn's disease.

Table 4. Some of the major and minor interactions of the biologic agents used to treat psoriasis

Drug	Major interactions (administering not recommended)	Minor interactions (monitoring recommended - may affect)
Anti-TNF	– Live virus vaccines – Other biologic agent	– Insulin and oral antidiabetic drugs (risk of hypoglycemia) – Antihypertensive drugs (amlodipine, nimodipine) – Statins (atorvastatin, simvastatin) – Benzodiazepines (diazepam, alprazolam) – Anticoagulants (warfarin)
Anti-IL12/anti IL23	– Live virus vaccines – Other biologic agent	– Methylprednisolone – Benzodiazepines (diazepam) – Oral contraceptives (ethinyl estradiol, etonogestrel) – Statins (lovastatin, atorvastatin) – Antihypertensive drugs (nicardipine, nifedipine) – Anticoagulants (warfarin)
Anti-IL17	– Live virus vaccines – Other biologic agent	– Anti-arrhythmic drugs (amiodarone) – Antihypertensive drugs (amlodipine, nicardipine) – Benzodiazepine (clonazepam, diazepam) – Oral contraceptives (drospirinone, norgestrel) – Statins (simvastatin) – Anti-HER2 (everolimus) – Anticoagulants (warfarin)
Anti-IL23	– Live virus vaccines – Other biologic agent	– Anti-arrhythmic drugs (amiodarone) – Antihypertensive drugs (amlodipine, nicardipine) – Anticoagulants (warfarin) – Opioid analgesics (methadone) – Benzodiazepine (clonazepam, diazepam) – Oral contraceptives (ethinyl estradiol, etonogestrel)

abortions and immunosuppression in the newborn is necessary.

Breastfeeding is considered safe during treatment with anti-TNF drugs, and this safety profile can be applied to anti-IL17 and anti-IL23 agents.³⁸

Male patients should be informed about the ability of anti-TNF agents to enhance fertilization capacity.

No alterations have been reported in the conception or development of fetuses resulting from fertilization by male patients under treatment with anti-TNF agents^{39,40}.

4. Erythrodermic psoriasis

Infliximab is the biological drug of choice to treat rapidly progressive and unstable erythrodermic psoriasis. Using this agent as a rescue drug is not recommended.⁴¹

5. Psoriatic arthritis

Anti-TNF drugs are recommended as first-line agents in the treatment of patients with severe psoriatic arthritis with or without severe skin involvement. Anti-IL17 agents, followed by ustekinumab, are recommended as second line of treatment. Treatment should be carried out in consultation with the rheumatologist.⁴²

6. Chronic viral diseases

- *Human immunodeficiency virus (HIV)*. Biologic agents can be used in HIV-positive patients with moderate to severe psoriasis resistant to conventional systemic treatments, in combination with

antiretroviral therapy (HAART). Using etanercept as first choice is suggested, although all anti-TNFs, ustekinumab, secukinumab and ixekizumab have been used with a good safety and efficacy profile. Treatment in close communication with the infectology department, and regular monitoring of viral load and for possible adverse effects is recommended.⁴³

- *Hepatitis B and C*. Before starting management with a biological drug, the specialist should be always consulted. Offering antiviral management before the start of treatment is recommended, and during its course, liver function should be monitored, as well as viral load.

Anti-TNF agents should be avoided in patients with hepatitis B virus infection, given that they have been associated with infection reactivation; ustekinumab would be the agent of choice, with low risk of viral reactivation, followed by anti-IL17 and anti-IL23 agents.

Data of studies suggest that anti-TNF agents can be used in patients with hepatitis C infection; in this regard, data on the use of ustekinumab are scarce and contradictory, and caution is therefore suggested. There are still no sufficient data regarding the use of anti-IL17 or anti-IL 23 agents in this context.⁴⁴⁻⁴⁹

7. Latent tuberculosis

Starting with ustekinumab or anti-IL17 agents is recommended in patients with latent tuberculosis who have completed at least one month of antifungal treatment. Etanercept is the anti-TNF agent with the lowest risk of reactivation^{50,51}.

8. Liver disease: steatohepatitis, cirrhosis

Anti-TNF agents and ustekinumab can be used with caution and in close communication with the specialist. Data so far suggest that anti-IL17 agents could also be used, with a good safety profile.^{52,53}

9. Organ transplantation

In general, using biological agents as third line is recommended in patients with transplants. Most these patients have been treated with etanercept, although there are already some reports of good response with a good safety profile with the use of ixekizumab⁵⁴.

10. Biologic agents in surgery

In low-risk surgical procedures, it is considered that anti-TNF agents and ustekinumab don't have to be discontinued in case of post-surgical infection. In procedures with moderate to high risk of complications (infection or negative impact on wound healing), the decision to continue or not with biological treatment should be individualized considering the type of procedure, patient comorbidities, disease severity and risk of exacerbation after discontinuation of the biologic agent, as well as concomitant medication.

In case discontinuation of the biologic agent is required before the procedure, three to five half-lives should elapse prior to the procedure: with etanercept, two to three weeks; adalimumab, six to eight weeks; infliximab, four to six weeks; ustekinumab, 12 weeks.

There are insufficient data to make specific recommendations regarding the newer agents: anti-IL17, anti-IL23.⁵⁵

11. Biologic agents in hemodialysis

Using of biologic agents as first line is recommended in patients with kidney disease and in those on hemodialysis (anti-IL17, ustekinumab and anti-TNF).⁵⁶

12. Biologic agents in cancer patients

In general, biologic agents, including anti-TNFs, ustekinumab and anti-IL17 agents, are not contraindicated in patients with a personal history of solid, hematological, or non-melanoma and melanoma skin neoplasms. The decision to start treatment with any biologic agent in a patient should be individualized and always in coordination with the oncologist.^{57,58}

13. Overweight and obesity

A negative effect of overweight on biological treatment has been demonstrated, except for infliximab,

which is the only drug that is dosed per kilogram of body weight, and thus it is the medication of choice in patients with morbid obesity.

Dose increase or dosing interval shortening can be considered in obese patients who fail to respond to standard doses (see optimization).⁵⁹

Conflict of interests

Dr. Podoswa has collaborated with Elly Lilly, Abbvie, Pfizer, Novartis and Janssen.

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