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Use of biological agents

Biyolojik ajan kullanımı

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Abstract

Biological agents are used to treat psoriasis in patients who do not respond to conventional systemic therapies such as cyclosporine, acitretin, methotrexate, phototherapy/photochemotherapy, or for whom these therapies are contraindicated. Patients who will use these agents are selected based on the eligibility criteria for biological agents. Patients are assessed at regular intervals with relevant laboratory parameters before and during the treatment. Patients should be assessed particularly for tuberculosis, malignancies, congestive heart failure, demyelinating diseases, and infections. All necessary vaccinations should be completed before starting the treatment, if possible. Live vaccines should be avoided during the treatment, and patients who require surgical intervention should be assessed for postoperative infection risk on a case-to-case basis, and the treatment should be suspended if deemed necessary.
Keywords: Biological agents, psoriasis, treatment

Öz

Biyolojik ajanlar siklosporin, asitretin, metotreksat veya fototerapi/fotokemoterapi gibi geleneksel sistemik tedavilere yanıt vermeyen ya da bu tedavilerin kontrendike olduğu durumlarda psoriasis tedavisinde kullanılırlar. Bu ajanları kullanacak hastalar biyolojik ajan için uygunluk ölçütlerine göre belirlenir. Hastalar tedavi öncesinde ve tedavi süresince uygun laboratuvar parametreleri ile belirli aralıklarla dğerlendirilirler. Hastalar özellikle tüberküloz, maligniteler, konjestif kalp yetmezliği, demiyelinizan hastalıklar ve enfeksiyonlar açısından değerlendirilmelidir. Tedaviye başlamadan önce mümkünse gerekli olan tüm aşılar yaptırılmalıdır. Tedavi esnasında canlı aşı yapılmamalı, cerrahi müdahale gerektiren hastalar postoperatif enfeksiyon riski açısından olgu bazlı değerlendirilerek gerekli görülen durumlarda tedaviye ara verilmelidir.
Anahtar Kelimeler: Biyolojik ajanlar, psoriasis, tedavi

General information

Biological agents are used for the treatment of patients with moderate to severe plaque psoriasis, unstable psoriasis and psoriatic arthritis who do not respond to systemic therapies such as cyclosporine, acitretin, methotrexate or phototherapy/photochemotherapy, or for whom these therapies are contraindicated or intolerable[1]. The eligibility criteria for the use of biological agents are the assessment criteria, also generally accepted in our country, in which psoriasis patients who are eligible for biological treatment are defined[2].

Eligibility criteria for biological agents

A) Quick worsening, involvement of visible areas, functional deficiency (palmoplanter, genital involvement, etc.) and presence of severe erythrodermic or generalized pustular psoriasis or joint involvement,

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B) In the presence of following conditions:
Patients who do not respond to conventional systemic therapies (where the disease cannot be kept under control with monotherapies or combination therapies involving appropriate systemic agents),
Patients in whom conventional systemic therapies are contraindicated or cause side effects (occurrence of toxicity or side effects in effective doses, patients at high risk of toxicity due to personal factors such as cumulative toxicity, age, gender, comorbidities, and potential drug interactions),
Patients who have rapid relapses (when the treatment is continuing or within 3 months after the treatment).

Assessment before and during biological treatment

Patients to be given biologics should be informed in detail about the benefits and possible risks of the drug and allowed sufficient time to evaluate them, and then their consent should be obtained. The treatment scheme and medication adherence should be stressed in particular[2].

Before starting the biological treatment, detailed anamnesis, physical examination, previously used drugs, and necessary laboratory tests should be evaluated to determine possible risk factors for the patient[1]. The type, duration and course of psoriasis, presence of arthritis, previously used therapies, their doses, durations, side effects, if any, efficacy, and reasons for discontinuing the medication should be recorded.

Additionally, other accompanying diseases, regularly used medications and the effect of the disease on quality of life should be questioned. Height-weight measurements of the patient should be carried out and their body mass index should be calculated. In their anamnesis, any acute and chronic infections, tuberculosis (TB), presence of demyelinating disease or malignancy in the patient, their family and first degree relatives should be investigated. Female patients should be assessed for pregnancy and the biological therapy should be started only after ruling out pregnancy through anamnesis and pregnancy tests. During the treatment, the patients should be monitored through detailed physical examination once a month in the first three months and quarterly thereafter. To decide on the continuation of the treatment, the patient should be assessed at week 12, and if there is response, the treatment should continue with quarterly monitoring.

A gastroenterology specialist should be consulted in patients with inflammatory bowel disease, for whom use of brodalumab, ixekizumab or secukinumab is planned[2,3].

Laboratory tests

Whole blood count, complete urinalysis, liver function tests, hepatitis markers, C-reactive protein, anti-HIV test, pregnancy test, chest X-ray, primarily interferon-gamma release assay (IGRA; quantiferon tbc test), and if not possible, tuberculin skin test, and protein purified derivative (TDT, PPD) should be conducted. These tests may be repeated at certain intervals during the treatment. More detailed tests may be needed depending on the clinical status, risk and exposure[1,2].

Tuberculosis

Patients who will use biological agents should be assessed for TB using anamnesis, physical examination, chest X-ray, PPD test (TDT test), and specific interferon-gamma (quantiferon tbc test) (IGRA) analysis. Prophylactic treatment against TB should be initiated if a TB sequel is present in the chest X-ray, there was close contact with a TB patient in the last one year (breathing the air in the same room for 24 hours), the person is a healthcare professional at high TB risk, the specific interferon-gamma (quantiferon tbc) test turned out positive or the initial TDT value was ≥5 mm. The prophylactic treatment should involve giving isoniazide (INH) 300 mg/day for 9 months even if the biological therapy was stopped. In cases when INH cannot be used, rifampicin may be used for 4 months. Patients receiving anti-tumor necrosis alpha (TNF) treatment should be examined every 6 months for TB (anamnesis, physical examination, radiological check) even if they are asymptomatic. Symptomatic patients should be examined for TB by a specialist regardless of any schedule. Patients who were prescribed a prophylactic therapy due to the sequelae found in their chest X-ray should be monitored for active TB before the anti-TNF treatment. When screening for latent tuberculosis infection (LTBI), either TDT or IGRA may be used. Both tests may give false negative or positive results. These tests may be positive in active TB and LTBI. Therefore, any of them turning out positive will not help differentiate between active TB and LTBI. When TDT is used as the initial test during an LTBI screening, indurations of 5 mm and more is considered as positive and a prophylactic therapy is prescribed. In patients with indurations less than 5 mm, an IGRA, or after 1-3 weeks, a booster TDT will be conducted. If the IGRA result is positive or the second TDT result shows indurations of 5 mm and over, prophylactic treatment will be initiated. If the second test is negative, a clinical decision will be made for prophylactic treatment. When IGRA is used as the initial test during an LTBI screening and the result turns out positive, prophylactic treatment will be prescribed. In cases where the result is unclear, repetition of IGRA or a TDT is recommended. If the result is negative, a clinical decision will be made for prophylactic treatment. IBRA should be preferred during a LTBI screening of patients with psoriasis for whom an anti-TNF therapy has been decided. Annual LTBI screenings will be appropriate for patients without LTBI. Another LTBI screening is not necessary in patients who were found to have LTBI. In patients whose LTBI test result is negative, the specialist may decide on a prophylactic treatment after considering the patient's risk status. If, during an anti-TNF therapy, TB is detected, treatment will be started in line with the national TB diagnosis and treatment guideline. The risk of TB may continue after the stopping the anti-TNF therapy. It would be appropriate to follow up on these patients in relation to TB for at least another 6 months. It is recommended to clinically monitor the TB status of the patients receiving a biological therapy every 3 months and until 6 months after the discontinuation of the therapy. Not only primary TB but also the extrapulmonary, atypical and disseminated forms of TB should be taken into consideration. It is mandatory in Turkey to fill out and send to the Ministry of Health a quarterly "Safety Follow-up Form" for the patients being administered an anti-TNF therapy and ustekinumab. The TB statuses of patients will be monitored with annual chest X-rays, and a quantiferon tbc test whenever needed. If suspicious conditions are found during these tests, more detailed tests such as

tomography should be conducted. During routine examinations, the physician should be cautious about fever and night sweating with unknown causes. A biological therapy may be started 2 months after the latent TB therapy[1-3].

Malignancy

Large-scale and long-term studies on psoriasis are not sufficient, but the risk of malignancy cannot be ruled out. Before starting a biological therapy, patients must definitely be assessed in terms of malignancy by taking anamneses very carefully and performing detailed physical examinations. Due to increased risk of malignancy, more caution should be taken in patients who had previously received 200 sessions of PUVA, 350 sessions of UVB or taken cyclosporine for more than 2 years without a break. Patients with a family history of malignancy also deserve more caution. Biological agents may be used in patients with solid organ tumours or non melanoma skin cancer who had been provided cure for more than 5 years prior to the treatment. Patients with psoriasis who use biological medication should be monitored for malignancies, and lymphoma in particular, during each visit with the help of anamnesis and physical examination. If any malignancy develops during treatment with biological agents, the treatment should be stopped immediately Table 1[4].

Pregnancy

The pregnancy category for anti-TNF agents and ustekinumab is B. However, since there are no randomized clinical studies on the use of biological agents during pregnancy and lactation, use of biological agents in these patients is not recommended. Contraception should be used in women with the potential of becoming pregnant during a biological therapy and for 6 months thereafter. If pregnancy occurs while on a biological therapy, the patient should be referred to a specialist to make a more detailed assessment and a joint decision should be made about the continuation of the biological treatment. The situation should be evaluated on the basis of the patient's status considering the benefit/harm ratio. Since the babies of mothers using anti-TNF during pregnancy may experience serious vaccine-related infections, administration of live vaccines including Bacillus Calmette Guerin to babies should be postponed until after month 6. As biological agents has no effect on sperm quality, contraception will not be needed for male patients. Biologics in the form of monoclonal antibodies with a long half-life are known to pass through the placenta starting from week 16. (See Special Cases).

Vaccination

Live vaccines should not be administered to adults receiving biological therapies and babies younger than 6 months. Any biological therapy should be discontinued 6-12 months before a live vaccine. The therapy may resume 4 weeks after the vaccination. If possible, the vaccines required for immunosuppressive patients should be reviewed and all vaccinations completed before starting the biological therapy[4]. Inactive vaccines may be administered while using biologics[3].

The babies of mothers who started receiving biological treatment after week 16 of their pregnancy should not be vaccinated before they become 6 months old[3].

Psoriasis patients who need to be vaccinated should receive all their vaccines at least 15 days before starting the biological treatment. Patients who are candidates for biological treatment are recommended to have their pneumococcus and influenza vaccines done before the treatment. Varicella zoster virus antibody may be checked in those with a history of negative or suspected varicella. Vaccination may be planned for patients who have not gained immunity. Treatment with a biological agent may be started 12 months after a herpes zoster vaccine[3].

Congestive heart failure

Anti-TNF agents are contraindicated in the presence of moderate to severe congestive heart failure (NYHA class 3-4). They should be used with caution in mild congestive heart failure (NYHA class 1-2). These patients should be monitored with electrocardiography, and if the ejection fraction is below 50%, they should not be given such agents. If new symptoms develop or the symptoms worsen, the treatment should be discontinued Table 1[2,4].

Demyelinating diseases

TNF-α antagonists should not be used in those who themselves or whose first degree relatives have a demyelinating disease. If, during the treatment, neurological symptoms suggesting a demyelinating disease appear, the treatment should be discontinued and a neurology specialist be consulted. These symptoms may include vision loss in one eye, painful eye movements, double vision, balance disorder, or Lhermitte's sign Table 1[3,4].

Hepatitis

A hepatitis B and C screening should be performed before starting a biological agent therapy.

There is an American Food and Drug Administration warning to avoid an anti-TNF therapy in patients with concurrent hepatitis B and C infections. While treatment can still be provided with regular monitoring in the presence of hepatitis C virus infection, it has been reported that if it must be used in the presence of hepatitis B virus infection, viral load along with liver function should be monitored before and during the treatment and until 3 months after the treatment[1,3].

HIV

A HIV screening should be performed before starting a biological treatment[1].

Chronic renal failure

Although there is not sufficient data, current literature data suggests that biological agents can be used with careful monitoring in patients with renal failure when absolutely necessary[1].

Surgical intervention

In patients to be administered elective surgery, the risk of postoperative infection should be weighed against the risk of discontinuing biological

agents and a decision should be made for each individual case. Using the drug should be suspended for a period 3-5 times the drug's half life or a period equal to the length between two doses, whichever is longer. The surgical team should be informed about the risk of infection. When the risk of postoperative infection goes away and wound healing is complete, biological treatment may be continued 1-2 weeks later if there are no complications[2].

In the case of an urgent surgical intervention, the agent will be stopped and the surgical operation will be carried out; when the patient returns to normal, the treatment will resume. There is no need to discontinue the treatment in minor burns and traumas. For extracting or treating teeth, the drug should be discontinued if the intervention is a major one; if it is a minor one, discontinuation of the drug may not be necessary. The situation should be evaluated for each patient individually based on the clinician's opinion[1].

Use in children and elderly

(See special cases)

Drug interaction

No interaction has been reported in the use of anti-TNF agents together with glucocorticoids, non-steroid anti-inflammatory drugs, analgesics, or methotrexate. However, due to risk of serious infection and neutropenia, anakinra should not be used with anti-TNF agents[1].

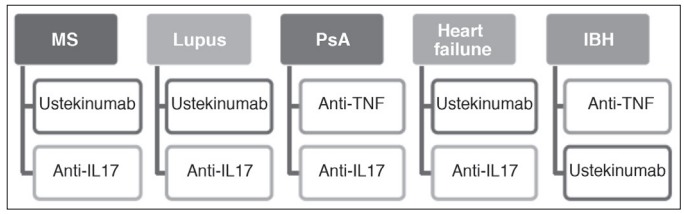
Laboratory examinations required before biological treatment and during follow-up

Time (months) → Test ↓	Start of treatment	Month 3	Month 6	Month 9	Month 12
Whole blood count	x	x	x	x	x
Complete urinalysis	x	x	x	x	x
Cementation	x	x	x	x	x
ALT, AST	x	x	x	x	x
Urea, creatinin	x	x	x	x	x
Glucose	x	x	x	x	x
PPD test	x				
Chest X-ray	x				x
Quantiferon test	x				x
CRP	x				
Pregnancy test	x				
Anti-HIV test	x				
HBV surface Ag-HBV surface Ab-anti-HBV core Ab-anti-HCV	x				
SARS-COV-2 RNA	x	In the presence of symptom or contact			

2,5-7

These tests may be conducted more frequently in cases deemed necessary by the physician.

Table 1. Suggestions of biologics based on comorbidities



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