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Genetic Engineered Preparations - An Innovative Approach in the Treatment of Rheumatoid Arthritis

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Abstract.
Currently, there are at least 20 genetically engineered drugs with different mechanisms of action used in the treatment of RA, and their number continues to increase every year. The use of genetically engineered drugs at an early stage of RA is of great importance, i.e. before the development of bone changes. In these cases, it is possible to develop remission for an indefinite period, which is tantamount to recovery. This paper provides information on the effectiveness of the use of genetically engineered drugs: rituximab, tocilizumab, alalimumab, infliximab in rheumatoid arthritis. Information on contraindications, method of administration, possible use during pregnancy and early rheumatoid arthritis is indicated.

Keywords: rheumatoid arthritis, genetically engineered drugs, rituximab, tocilizumab, infliximab, adalimumab, pregnancy.

Rheumatoid arthritis (RA) is a progressive autoimmune disease with predominant damage to the joints and internal organs and leading to disability 10 years after the onset of the disease in about half of cases. Despite significant advances in treatment, the problem of treating RA is still urgent. Initially, the high hopes placed on basic drugs (methotrexate, sulfosalazine, cyclosporine, azathioprine, delagil) did not fully justify, because in a number of cases proved to be ineffective, and due to the presence of side effects or severe anemization, they turned out to be inapplicable [2,4]. But with the disclosure of the mechanisms of immunopathogenesis of the disease and the development of immunopharmacology, a fundamentally new class of drugs appeared - genetically engineered drugs, which are superselective immunoblockers that block a specific link in immunopathogenesis, making it impossible for the development of the disease for some time, and at an early stage - contribute to the development remission for an indefinite period and even the reverse development of the disease, which is tantamount to recovery [1,3].
Currently, there are at least 20 genetically engineered drugs with different mechanisms of action, and their number continues to increase every year [5, 10]. Not all drugs are registered in Uzbekistan and, accordingly, are used for treatment in our conditions. In this regard, we provide our own melon about the drugs that are present in the market of Uzbekistan [6,7].
Infliximab (remicade) is the oldest genetically engineered drug used for the treatment of RA and appeared in 1995.The drug blocks the production of tumor necrosis factor (TNF), which is produced in large quantities by immune cells, as a result of which one of the most important links in the immunopathogenesis of the disease is blocked and remission develops. As a

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result of its use, the inflammatory activity is significantly reduced, the swelling of the joints is stopped, the pain syndrome decreases, the range of motion in the regulations increases [9,11]. There is a positive laboratory dynamics: the level of ESR, C-reactive protein decreases or normalizes, the phenomena of anemization decrease or stop. Indications for the use of infliximab are a high degree of RA activity, lack of efficacy from the basic therapy, severe anemization, which prevents the use of immunosuppressants. N. like all genetically engineered drugs, remicade has its own contraindications for use:

1. Tuberculosis, both active and in history
2. HIV infection
3. Hepatitis B, C and D, syphilis
4. The presence of an infectious and inflammatory process in the body (chronic pyelonephritis, tonsillitis, chronic bronchitis, etc. before the relief of inflammatory manifestations.)
5. Dropped polyvalent drug allergy
6. All somatic diseases in the stage of severe decompensation
7. The presence of concomitant mental disorders, dementia
8. Period 2 weeks before and after planned surgical treatment.

Due to the fact that the drug is obtained by genetic engineering methods, by combining human and mouse molecules and being a high-molecular-weight protein compound, the drug is reactogenic, i.e. development of allergic and pyrogenic reactions is possible during its administration, in connection with which predication is necessarily used - preliminary intravenous drip administration of 2 ml of dexamethasone per 100 ml of saline, and if necessary, if a reaction develops during administration, administration of calcium gluconate, suprastin, analgin is used and diphenhydramine. The drug is administered slowly at a dose of 100 mg per 200 ml of saline solution for 2 hours. The frequency of development of reactions with the introduction of the drug reaches 20%.

It should be borne in mind that due to the extreme complexity of the immunopathogenesis of RA, in many cases the use of infliximab turns out to be ineffective, due to the fact that other mechanisms of RA development are involved in a particular patient, and not only TNF hyperproduction. This phenomenon has been known since the beginning of the 2000s, which served as further research in the field of creating new genetically engineered drugs with a different mechanism of action. In addition, the development of antibodies to infliximab is possible (the development rate reaches 10%), which makes its use with prolonged administration senseless and poses the threat of anaphylactic shock [8].

That is why infliximab is used to a limited extent for the treatment of RA, giving way to other genetically engineered drugs. The authors have a positive experience of using the drug in 20 patients with RA. Against the background of its use, relief of signs of inflammation, relief of signs of inflammation in the joints, a significant improvement in quality of life indicators were noted [12,13].

Another genetically engineered drug widely used in the treatment of RA is adalimumab (humira), an interleukin 4 antagonist that plays an important role in the development of RA immunopathogenesis. The drug has been used since 2004. Currently, it has been reliably proven that the use of adalimumab inhibits the development of RA [14, 15]. The drug is administered subcutaneously at a dose of 40 mg. It is well tolerated and, when administered, there is practically no development of adverse reactions. No premedication is required and patients, with

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proper adherence to all conditions, can enter it themselves. The drug can be widely used in the outpatient treatment of RA. Due to the fact that the drug is completely humanized, the risk of developing reactions is extremely small. The frequency of development of antibodies to adalimumab is currently not precisely known, but it is assumed not to exceed 0.1%. However, the drug turns out to be ineffective with a high degree of RA activity, and has proven itself well in patients with a minimal degree of disease activity and for maintaining remission. Despite the fact that according to the instructions, the drug should be injected every 2 weeks, due to the cost, the authors have a positive experience of administration with an interval of 2 months. To date, there is experience of using adalimumab in 50 patients with RA, against the background of which there is a stable remission. Contraindications for use are the same as for infliximab.

With the development of our knowledge about the immunopatonegesis of RA, the important role of interleukin 1, which takes an important part in the processes of joint destruction, became clear. In this regard, the use of the interleukin 1 antagonist - tocilizumab (actmra), which has been used in treatment since 2007, has become very important. Unlike other genetically engineered drugs, it is administered depending on the patient's weight, according to the formula. The drug is administered by intravenous drip in 100 ml of saline solution or subcutaneously. It is usually well tolerated and does not require premedication when administered. In rare cases, minor reactions are possible, which are easily stopped. The drug is completely humanized and therefore the incidence of antibodies to tocilizumab is extremely low and is currently not known for sure. There is experience of use in 100 patients with RA. Against the background of its use, a significant improvement in the condition, normalization of indicators of inflammatory activity, and an improvement in the quality of life were noted. Contraindications to the use of tocilizumab are the same as for other drugs - TNF inhibitors.

Since the mid-80s of the last century, the fundamental works of Panay revealed the leading role of B cells in the immunopathogenesis of RA. In 1998, a drug was created - a B-cell blocker - rituximab (mabthera, reditus, acelbia), originally intended for the treatment of B-cell lymphomas, but since 2000 it has been used in the treatment of RA. Over the past 20 years, a huge experience of its application has been accumulated in the world. As a specific blocker of B-lymphocytes, the drug blocks these cells, making it impossible for the further development of RA. Currently, the inhibitory role of rituximab in relation to bone destruction and even the ability to reverse the development of bone changes in RA has been reliably proven.

Over the years of using the drugs, how much have the administration regimens changed? The statement about the introduction of a dose of 1000 mg with a two-week interval and subsequent administration at 25/52 weeks of treatment was replaced by more flexible drug administration regimens. Currently, the drug is administered under the control of the number of B cells. This is all the more important because B cells play an important role in the anti-infectious defense of the body, and their complete long-term "shutdown" is unsafe in relation to the risk of developing a banal infection. This is why the β-cell count is reduced to about 400 per ml. The drug is a chimeric compound - a combination of a human and a mouse molecule and is a highly reactogenic compound. Therefore, it is used only in stationary conditions. Premedication is mandatory: 100 mg of methylprednisolone or 2 ml of dexamethasone injected intravenously and 2 ml of suprastin, after which the drug itself is injected. A dose of

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500-1000 mg is injected intravenously over 3 hours per 500 ml of saline solution, a dose of 100 mg is injected per 200 ml of saline over a period of 1.5 hours.

However, despite the premedication, in about 30-35% of cases, allergic, pyrogenic and other side reactions may develop that occur during the administration of the drug. It should be borne in mind that with the development of the reaction, the administration of rituximab is not stopped, but only stopped, the reaction is stopped (side effect, for example, a hypertensive crisis) and its further administration is continued. In most cases, the reactions are quickly stopped, although the development of severe reactions requiring intensive therapy has been described. It should also be noted that the drug is administered under aseptic conditions, i.e. the room must be quenched.

In order to reduce the risk of complications during the administration of the drug, the patient must be carefully examined for contraindications similar to TNF inhibitors. In addition to the listed contraindications (as with TNF inhibitors), leukopenia, lymphopenia, and the presence of a viral load in the body are also added. The introduction of the drug is postponed in the presence of symptoms of acute respiratory viral infections (influenza), as well as menstruation in women. An interesting feature was noted by the authors: in hypertensive patients, there was a tendency towards a decrease in blood pressure. It should be noted that the administration of the drug is meaningless when the level of B-cells is less than 400, because with a small number of B cells, the effect of rituximab does not occur (there are no target cells for its action).

The authors have experience of using rituximab in more than 220 patients with RA with good effect. Despite the fairly frequent development of adverse reactions at the time of administration, the results of the application were good. The patients showed a decrease in the parameters of the inflammatory process or their normalization, relief of pain in the joints, an improvement in the quality of life, which persisted for 6-20 months of observation.

It should be noted that an important feature of the drug -0 is the very frequent formation of antibodies, which are formed in about 1.5-3% of cases with its regular administration, and now there are methods for the determination of anti-ab-antibodies.

The use of genetically engineered drugs at an early stage of RA is of great importance, i.e. before the development of bone changes. In these cases, it is possible to develop remission for an indefinite period, which is tantamount to recovery.

In conclusion, an important issue should be sanctified about the possibility of using genetically engineered drugs during pregnancy and lactation. RA is a widespread disease, occurring in about 1% of the entire population. Naturally, there are many young women with RA who want to have children or who developed the disease after childbirth. The use of these drugs is possible, Firstly, these drugs are very large protein molecules (with a molecular weight of hundreds of thousands of kilodaltons), and cannot penetrate the placenta and, therefore, affect the developing fetus. During lactation, for the same reasons, the possibility of their excretion in the mother's milk will be extremely small, and even their oral ingestion into the child's body is safe, because the existing, albeit not fully formed digestive system, is capable of splitting these molecules into separate protein fragments that do not pose a danger to the child's body. This is their advantage over other drugs. Which are excreted in milk and most of the drugs used in the treatment of RA cannot be used during pregnancy and lactation [13].

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Thus, despite the fact that a small number of genetically engineered drugs are registered in Uzbekistan, modern treatment of RA is possible, which made it possible to effectively control its course, achieve long-term remission and avoid the development of disability. I would like to hope that the number of genetically engineered drugs will increase in the future.

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