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Thebenefitsof the combined therapy by infliximabe and methotrexate in patients with rheumatoid arthrits

PogrebnayaM.V., Eryomenko S.I.

Amur state medical academy, Russia

Abstracts. Rheumatoid arthritis is a chronic progressive immunoinflammatory disease which mainly affects joints and leads to disability frequently of young people. In all cases it is almost impossible to induce complete remission. That's why the treatment by basic anti-inflammatory drugs should be prescribed as early as it possible, during first six months since disease had been diagnosed. Comparative evaluation of the monotherapy by methotrexate, infliximabe has shown that combination of basic anti-inflammmatory drugs is more effective, such combined therapy decreases clinical-laboratory activity and rate of bone destruction.

Key words: rheumatoid arthritis, basic therapy infliximabe, methotrexate

Rheumatoid arthritis (RA) is a wide spread chronic inflammatory disease which mainly affects joints, and the prevalence trembles from 0.5 to 1.0. According to the official statistics in 280 thousands (260 are adults and 20 are children and teens) of patients with RA had been registered in Russian Federation, 2002. Among all patients there are about 26 thousands had been revealed for the first time. Approximately 90% of patients will loose their ability to work and 1/3 of them become fully disabled persons through 10-15 years since the beginning of the disease. In Russian Federation the middle age of persons with RA who are disabled is about 48 and more then 25% of patients need in expensive drug and surgical management (1,4,5).

The aim of RA pharmacotherapy is to gain complete and if it's not possible - partial remission. There are a lot of remedies which can be used for RA treatment and all of them called basic anti-inflammatory drugs (BAID) because such drugs help to decrease the RA activity, to improve functional condition and to slow down destruction of the joints.

American college of rheumatologists recommends BAIDs for RA treatment and called BAIDs as "disease modifying anti-rheumatic drugs" which were reviewed in 2008. It is necessary to count the duration of RA (less then 6 months, 6-24 months, more the 24 months), RA activity and prognostic factors (functional restrictions – HAQ disability index, extra-joint manifestations – vasculitis, Sjogren's syndrome, lung-involvement, positive rheumatoid factor or cyclic citrulline protein antibodies, or/and erosive roentgenologically proved bone changes) while the prescribing of "first line" therapy drug.

Even the here and now, Methotrexate (MTX) is a "golden standard" among all BAIDs, it can be used for mono- or combined therapy with other BAIDs or even biological drugs. However as it has been told complete or partial remission is a rare result (1,2,5) that's why RA pharmacotherapy is one of the difficult problem of clinical medicine which stimulates pharmaceutical companies and doctors on a search of new approaches in the treatment (2,3).

According to the modern treatment protocols, to achieve this aim it is necessary to begin the treatment by BAIDs as early as it possible, the desirable time is first six months (2,3,6,7,8). During last years a group of biological genetically engineered drugs (BGED) has been developed. The inhibitors of tumor necrosis factor (TNF-α) are most important specimens of this group. TNF-α is a

cytokine which determines the development of sinovial inflammation and osteclast-induced bone destruction in patients with arthritis.

Such drugs as infiximab, adalimubab, rituximab are monoclonal antibodies which can bind TNF-α and neutralize it proinflammatory effects. BGED are drugs of the "second line" therapy, i.e. it can be used when "first line" therapy drugs are not effective. The new aspect of American recommendations in treatment of patients with RA is changing of infiximabe, role (INF) (Remiceid, MSD). INF is the selective inhibitor of tumor necrosis factor (anti-TNF) and it has powerful anti-inflammatory and immunosuppressive effects. Although the effectiveness and safety of this drugs have been estimated long ago (INF has been developed specially for RA treatment and first investigations have been finished in 90^{th} years of the last century) though it has been valued as "second line" therapy drug for a long time. However ACR recommendations of 2008 attribute INF to the "choice drugs". Experts recommend it to use in patients with different variants of RA: with low activity, high activity, early and chronic RA, with unfavorable prognostic factors and without it.

The combination of INF with MTX has been recognized as possible. Monotherapy by any BAID is not able to control the bone and joint destruction and can induce the remission very seldom, that's why the most effective way to control and induce the remission is to combine BAIDs (2,3,9,10). The combined therapy conception is based on the fact that BAIDS can have complementary mechanisms of action which determine most powerful effect to pathogenetic chains in rheumatoid inflammation. (2,3,4,9,10).

Combined therapy by INF and MTX theoretically proved well (9,10,11) and the effectiveness is more higher then the same one during monotherapy and there is no growth of side effects, but potentially dangerous side effects such as leucopenia and liver toxicity can affect patients more frequently.

The aim of this work is to compare the effectiveness of INF monotherapy, MTX monotherapy and combined therapy by INF and MTX in the achievement of clinical and laboratory remission in patients with RA (RA activity, the rate of functional and bone-destructive lesions).

Materials and methods.

In the conditions of rheumatologic department (Amur regional hospital) 102 patients were examined and enrolled in the investigation of combined therapy effectiveness (some pathogenetic drugs). The majority of the examined patients is woman (78 (76,5%) patients), 24 (23,5%) patients were men. The age of the patients varies from 20 to 68, middle age is 42,6±12,8 years. The duration of the disease varies from 6 mon. to 22 years and the average mean is 14,8±8,2 years. First group of patients (18 persons) received basic therapy by infiximabe; second group – 58 patients received basic therapy by methotrexate in variant doses from 10 to 17,5 mg per week. And the third group – 26 patients received combined drug therapy (INF and MTX), 10-20 mg per day and 7,5-12,5 mg per week correspondingly.

Examination has been performed before, after the treatment and after 3, 6, 12, 18 and 24 months. The criteria of the American rheumatologic association have been used to diagnose RA, 1987. Inflammation activity and the effectiveness of the therapy were estimated before and after the treatment according to such parameters as: joint pain intensity (visual-analogue scale), morning joint stiffness (min), duration of indisposition (min), and the number of inflamed and swollen joints, functional activity, the progression of the disease; dynamics of clinical symptoms (DAS 28), laboratory activity (erythrocyte sedimentation rate, C-reactive protein, etc.); immunologic investigation (immune status, ACCP, rheumatoid factor), US-investigation of joints, roentgenography – twice per year, MR-imaging of joint. Activity of RA has been estimated according to disease activity score – DAS 28, which includes Riche's joint index, swollen joint number, ESR, general health condition and general disease activity according to the patient's point of view (visual-analogue scale).

Disease activity score was estimated as $0,56x \sqrt{(\text{painful joint number28}) + 0,28x\sqrt{(\text{swollen joint number 28}) + 0,70x\ln(\text{ESR}) + 0,014x}}$ general health condition.

The evaluation of antirheumatic therapy was carried out according to European antirheumatic league criteria – ACR20, ACR50, ACR70 which is correspond with 20%, 50%, 70% improvement of painful joint number, swollen joint number, HAQ, general health condition, ESR, CRP. Thesafetyofthedrugtherapyhasbeenestimatedwith the counting of side effects which affected patients.

Resultsanddiscussion.

Theevidentinflammatoryprocess has been observed clinically in all groups, but the most evident inflammation took place in patients of the 3d group. Duringtheactivityjointdefiguration, constant joint deformations took place in patients. SeropositiveRA (78% ofpatients) characterizedbysymmetric lesions of small hand and foot joints mainly with following involvement of new joints, including medium and large joints. Seronegative RA (22% of patients) usually started from asymmetric mono- oligoarthritis of large (genual) joints with following involvement of intercarpal, carpometacarpal, radiocarpal joints, and appearance of process symmetry. In 89% of patients with seronegative RA after the certain time it was possible to reveal rheumatoid factor in variable titers which rise up according to progression of the disease. 11% of patients were seronegative during the whole period of investigation. Patientswithseronegativeandquiteoftenseropositivearthritis received sulfasalazalone in the beginning of the disease (2-3 g per day), then sulfasalazone was changed to MTX, INF or its combination because of high activity and rapid progression. Thenonspecificindexesofacuteinflammation (ESR, CRP, leucocytosis, sialic acid, hyperfibrinogenemia, etc.) and ACCP (cyclic citrulline protein antibodies) were elevated mainly in patients with third and second rates of activity and less in patients with first activity rate of RA. According to clinical and laboratory activity all patients were divided into 3 groups: high activity rate (III) – DAS >5,1 - 58,8 % of patients, medium activity rate (II) - 37,3 % and low activity rate – DAS <3,2 - 3,9 % of patients.

In all groups immunological disorders have been revealed. Most frequent disorders such as imbalance of cell and humoral immunity, immunoregulatory imbalance with the deficiency of cytotoxic T-cells were observed in 82,4% of patients with RA in all groups. The increasing of immunoregulatory index has been revealed in 63,7% of patients. Theimmunoglobulindisproportionalso has been observed in patients with RA: the increasing of IgM – 63,7%, IgG – 58%, IgA – 18% of patients. Also all patients had had a complement imbalance.

Roentgenological changes were noticed in all patients, but significantly in second and third groups. Activity of the process didn't correlate usually with the rate of destructive lesions which were measured roentgenologically. 40 patients (39,2%) had a persistent laboratory activity in spite of the drug therapy, but roentgenologically this patients had a second stage of bone the destruction. First stage (Steinbroker) wasn't revealed in this group, second stage – 40 patients (39,2%), third stage – 48 patients (47,1%), fourth stage – 14 patients (13,7%). The results of US-investigation, MR-imaging, roentgenograms have been assumed and compared to estimate the progression of the disease. MR-imaging has shown the best ability to reveal early cartilage erosions. The comparison of three groups has shown that third group (INF +MTX) had had the best dynamics of clinical and laboratory activity (< painful joint number, swollen joint number, ESR, CRP), also the general health condition and DAS parameters improved quicker than the same parameters in other groups. Also the immunological disorders were less then in other groups. In the same group there were more patients with ACR 70%, 50% as the reflection of the drug therapy effectiveness.

Side effects have been noticed in all groups: 18% of patients had digestive disorders, hair loosing, skin manifestations, headache (3 patients); patients who received MTX had also digestive disorders, stomatits, eruption, liver lesions, myelodepression (9 patients); sulfasalazone induced digestive disorders, leucopenia, and liver enzymes growth (3 patients).

The effectiveness of the drug therapy was better in patients who primary received INF then in patients who received INF after the course of MTX therapy. That's why INF can be named as

“first line” therapy drug along with MTX, especially in patients with clinical, laboratory and instrumental predictors of unfavorable prognosis.

Monotherapy can’t effectively control the joint destruction and recently induces remission. Combined therapy by INF and MTX in patients of the 3d group has shown sufficient effectiveness, good tolerance, and same rate of side effects, the tolerance of combined therapy wasn’t differ from the monotherapy by INF or MTX. Itisnecessarytocarryoutcarefulmonitoring of side effects if the patient has a risk to be affected. Such risk factors were bad BAIDs therapy tolerance in the past, high HAQ mean, extra joint manifestations, co-morbidity.

Combined therapy should be started with caution if the patient has liver lesion, arterial hypertension, and other cardio-vascular diseases.

Thus, early INF administration and combined therapy by INF and MTX have the great benefits for the prognosis improvement in patients with severe active RA and some advantages behind other combinations of disease-modifying drugs.

Conclusions

1. Comparative estimation of BAIDs effectiveness has shown the dominating effectiveness of INF, especially in patients with clinical, laboratory and instrumental predictors of unfavorable prognosis.
2. INF monotherapy is not able to control joint destruction effectively and recently induces remission.
3. The best effectiveness has been shown by the combined therapy (INF and MTX).
4. Combined therapy is a chance for patients who are indifferent to monotherapy be INF or MTX and who have rapid joint destruction.
5. Combined therapy induces the same rate of side effects as monotherapy by INF or MTX.

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Anatomical and histological features ventilation phrenic department of the left lung of rats

Popov S.V.[1], *Zinov'ev S.V.* [1], *Tseluyko S.S.*[1] , *Zhou X.D.* [2], *Li Q.* [2]

Amur StateMedicalAcademy, Blagoveshchensk, Russian Federation
The Second Affiliated Hospital of Chongqing MedicalUniversity, China

Abstratcs: For the purpose of the study was to investigate the anatomy of the left lung ventilation in rats. At 100 rats were studied cryostat and paraffin sections of the lung. Additional sections were stained with alizarin red and potassium antimonate. At the root of the left lung rats revealed cranial and caudal lobar bronchi. At the root of the left lung of rat discovered the mouth of the cranial and caudal pulmonary veins pool. Caudal lobe bronchus of the left diaphragmatic vents rat lung. When histochemical study in the terminal bronchioles is found expressed extima that prevents spadenie distal airways.

Key words. The left lung of rat, caudal lung bronchi, terminal bronchioles, extima.

Features of the structure of the rats described in the classical guidelines [5,6]. Rats are a classic model for the study of stress. Rat lung and trachea is investigated in order to study the mechanism of the impact of the adverse effects of the environment on the body. At the same time, the anatomical features of rat lung ventilation remains poorly understood aspect in the high resistance of rats to the effects of the pathogenic factors of the environment. For bronchospasm characteristic spadenie mucosa resulting in a strong deformation of the lumen of the small airways and terminal bronchioles. We are in their studies found no effects of bronchospasm distal airways during prolonged general cooling of rats at a temperature of 15^0 C [4]. In the lungs there are changes in focal light of terminal bronchioles shown desquamation mucosal epithelium [3,7]. This indicates the presence of rats morphological mechanisms that prevent bronchospasm distal airways. The study of these mechanisms is necessary to assess the representativeness of the results of the study of general hypothermia. The left lung of rat arranged easier than the right, it is easier to learn on the purpose of our study was to investigate the anatomy of the left lung ventilation in rats.

Materials and methods:

The experimental animals were housed in standard vivarium conditions Amur State Medical Academy. The object of the study were white mongrel male rats weighing 200-240 grams of 100 animals. For the overall histology lungs of experimental animals were fixed in formalin. After production of cryostat sections of lung stained with hematoxylin eosin Ehrlich. After staining of lung slices on a freezing microtome histological sections were made of light, a thickness of 15 microns. Histological sections were glued on gelatinized slides. Morphometric study of the lungs of rats was performed using the software-Optics Pro (Italy).

Additionally, we performed histochemical study of the rat lung. In order to study the localization of sodium ions and other cations, we stained lungs antimonates by Shiina, Midzuhira, Amakava and Futesaku [1,4]. After staining of lung slices on a freezing microtome histological sections were made of light, a thickness of 15 microns. Histological sections were glued on gelatinized slides. Cryostat sections of lung counterstained Azur 2. Additional histochemical detection of cations was carried out in a 5% alcoholic solution of alizarin red for 24 hours. [2]

Results and discussion

Easy rats incorporates pneumatic and respiratory part.