MANAGEMENT OF RHEUMATOID ARTHRITIS IN BULGARIA - FOCUS ON THE REQUIREMENTS FOR INTRODUCING BIOLOGIC THERAPIES TO PATIENTS AND CURRENT PRACTICES OF CLINICIANS

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Patients with Rheumatoid Arthritis in Bulgaria

- Lack of epidemiological data on the prevalence of rheumatoid arthritis in Bulgaria
- It is estimated that more than 60,000 patients are suffering from Rheumatoid Arthritis in Bulgaria
  - 3% of them are children
  - Most of the patients are of active working age, between 35 and 50 years
  - Women are about three times more than men

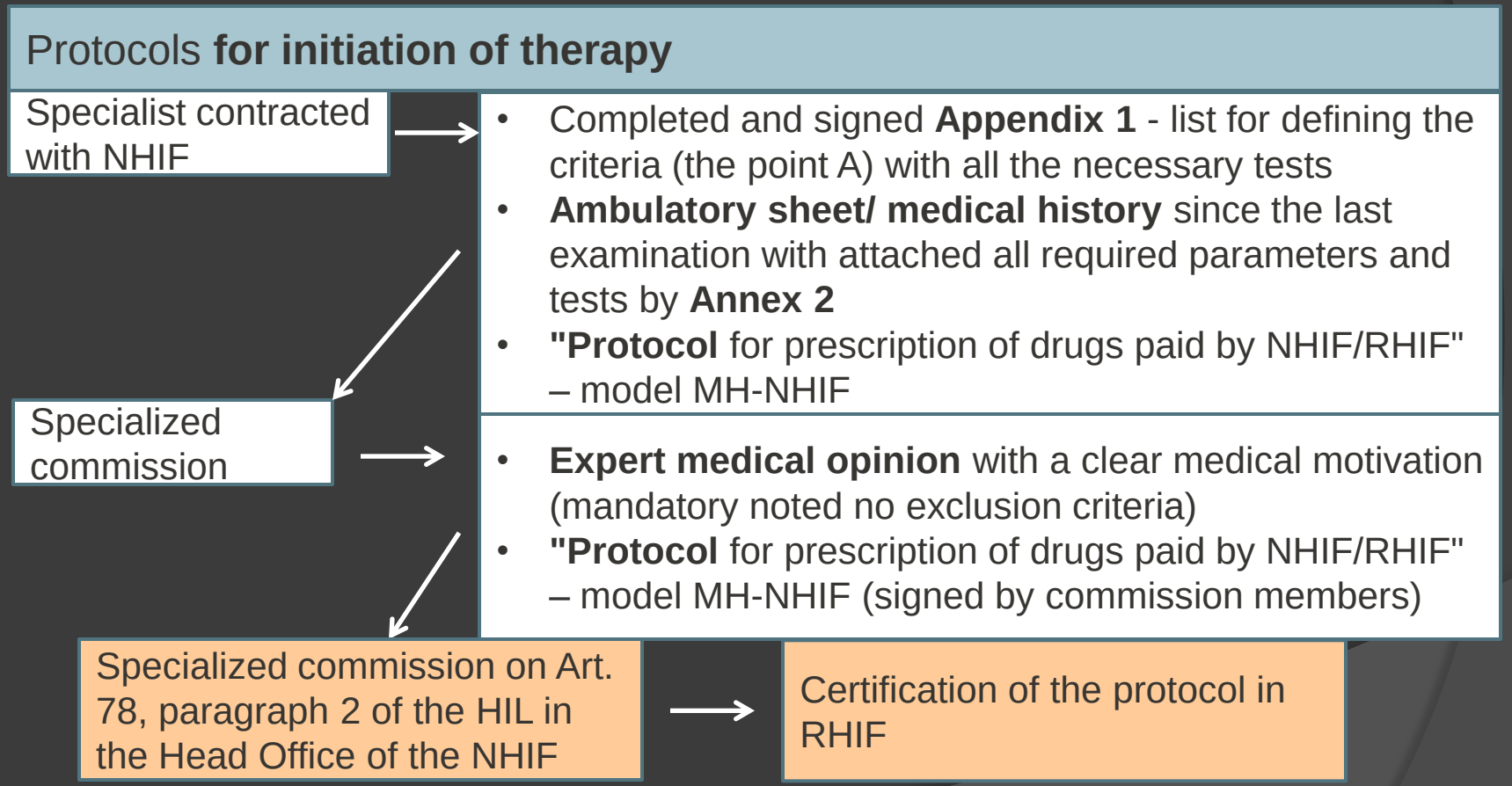
Initiation of treatment with biologic agents - Specifics

- Outpatients rheumatologists can not initiate treatment of RA with biologics.
- Outpatient rheumatologists (with NHIF contract) can send patients with RA to rheumatology centers with proposals for treatment with biologics.
- The protocol is issued by specialists with specialty codes 20 - Rheumatology, working under contract with the NHIF
- Expert medical oppinion is issued only in three specialized commissions: in Sofia, Plovdiv & Varna.

Initiation of treatment with biologic agents - Specifics

- For gaining first prescription with biologic, patients have to wait around 1-1,5 months
- Every new prescription of biologic has to be approved at National Level of NHIF
- The updated Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care (active from 15.03.2013) are still very strict for initiation of biologics
- Level of reimbursement: 75%, the rest 25% are covered by the pharmaceutical companies

Order for validation of protocols



Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

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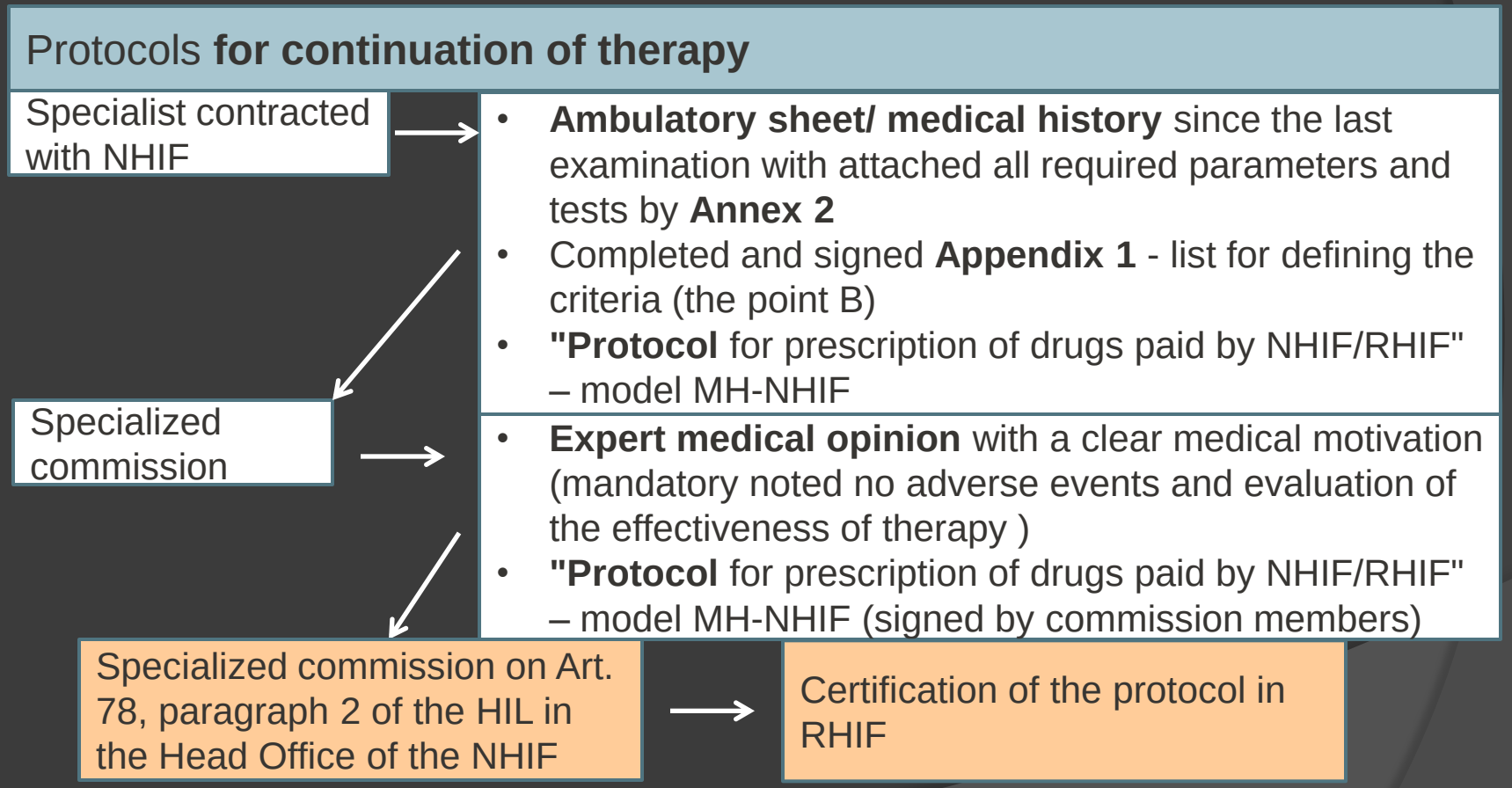

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

General rules

- Insured person shall submit prepared documents in RHIF, the territory of which she/he made the choice of GP. The documents include:
  - Application to the Director of the RHIF
  - Completed and signed Appendix 1
  - The full examinations set (physical, instrumental and laboratory), as marked in Annex 2
  - Protocol for prescription of drugs paid by NHIF/RHIF

- RHIF accept documents by point 1 after checking health insurance status of the insured person
- The first and each subsequent protocol are issued for a period of six months

Criteria for initiation of first course (all criteria are mandatory) with anti-cytokine drugs

	MKB M05, M08						
1	**Confirmed diagnosis** - presence of 4 or more criteria of the following 7, according to American College of Rheumatology (ACR) 1987: • Morning stiffness , lasting more than 30 minutes • Arthritis of 3 or more joint areas • Arthritis of hand joints • Symmetric arthritis • Rheumatoid nodules • Rheumatoid factor • Radiographic changes for RA	2	**DAS28**>5.1	3	Refractoriness from DMARDs (methotrexate, leflunomide, sulfasalazine and others as a monotherapy or combination therapy with glucocorticoids) in optimal courses and doses for at least 6 month period. Therapy should have been unsuccessful from at least two of them, one must be methotrexate at a weekly dose of 20 mg.	4	**Lack of exclusion criteria***

MKB M05 - Seropositive rheumatoid arthritis
MKB M08 - Juvenile rheumatoid arthritis

Criteria for continuation of treatment (all criteria are mandatory) with anti-cytokine drugs

	MKB M05, M08				
1	**Change of parameters:** • Swelling of the joints and morning stiffness - reduction of at least 50% and retention in time • Number of tender and swollen joints - reduction of at least 50% and retention in time • ESR – under 40 mm or CRP – negative and retention in time	2	Total score of parameters - reduction of DAS28 **with more than 1.2 and retention in time**	3	**Lack of adverse event and exclusion criteria**

MKB M05 - Seropositive rheumatoid arthritis
MKB M08 - Juvenile rheumatoid arthritis

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Excluding criteria (in initiation continuation of treatment)

1. Pregnancy and lactation
2. Active and latent tuberculosis
3. Acute of chronic viral hepatitis
4. Neoplastic diseases
5. Congestive heart failure class IV NYHA
6. Aplastic anemia, Expressed granulocytopenia, Myelofibrosis, Lymphoma
7. Multiple sclerosis and other demyelinating diseases
8. Lack of therapeutic effect at week 12 after initiation of treatment (duration of morning stiffness, joint swelling, number of tender and/or swollen joints, ESR and CRP)
9. Discontinuation of treatment attributable to patient for a period of more than two months
10. Inclusion of the insured person in clinical trial

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Criteria for initiation of first course (all criteria are mandatory) with tocilizumab

	MKB M05, M08						
1	**Confirmed diagnosis** - presence of 4 or more criteria of the following 7, according to American College of Rheumatology (ACR) 1987: • Morning stiffness , lasting more than 30 minutes • Arthritis of 3 or more joint areas • Arthritis of hand joints • Symmetric arthritis • Rheumatoid nodules • Rheumatoid factor • Radiographic changes for RA	2	**DAS28**>5.1	3	Refractoriness from DMARDs (methotrexate, leflunomide, sulfasalazine and others as a monotherapy or combination therapy with glucocorticoids) in optimal courses and doses for at least 6 month period or TNF antagonists. Therapy should have been unsuccessful from at least two of them, one must be methotrexate at a weekly dose of 20 mg.	4	**Lack of exclusion criteria***

MKB M05 - Seropositive rheumatoid arthritis
MKB M08 - Juvenile rheumatoid arthritis

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Criteria for continuation of treatment (all criteria are mandatory) with anti-cytokine drugs

	MKB M05, M08				
1	**Change of parameters:** • Swelling of the joints and morning stiffness - reduction of at least 50% • Number of tender and swollen joints - reduction of at least 50% • ESR – under 40 mm or CRP – negative or below 8 g/l	2	Total score of parameters - reduction of DAS28 **with more than 1.2 and retention in time**	3	**Lack of adverse event and exclusion criteria**

MKB M05 - Seropositive rheumatoid arthritis
MKB M08 - Juvenile rheumatoid arthritis

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Excluding criteria (in initiation continuation of treatment) – tocilizumab

1. Pregnancy and lactation
2. Active severe infections
3. Neoplastic diseases
4. Absolute neutrophil count (ANC) below 2 x 10^9/l
5. Lack of therapeutic effect at week 12 after initiation of treatment (duration of morning stiffness, joint swelling, number of tender and/or swollen joints, ESR and CRP)
6. Discontinuation of treatment attributable to patient for a period of more than two months
7. Inclusion of the insured person in clinical trial

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Monitoring

INN	Before starting*	Control on 6 months**
Etanercept	Chest X-ray, joints x-ray, RF (for M05), tuberculin test, hepatitis markers CBC, ESR, CRP, ASAT, ALAT	CBC, ESR, CRP, ASAT, ALAT
Adalimumab	Chest X-ray, joints x-ray, RF (for M05), tuberculin test, hepatitis markers CBC, ESR, CRP, ASAT, ALAT	CBC, ESR, CRP, ASAT, ALAT
Certolizumab	Chest X-ray, joints x-ray, RF, tuberculin test, hepatitis markers CBC, ESR, CRP, ASAT, ALAT	CBC, ESR, CRP, ASAT, ALAT
Golimumab	Chest X-ray, joints x-ray, RF (for M05), tuberculin test, hepatitis markers CBC, ESR, CRP, ASAT, ALAT	CBC, ESR, CRP, ASAT, ALAT
Tocilizumab	Chest X-ray, RF (for M05), tuberculin test, hepatitis markers CBC, ESR, CRP, ASAT, ALAT, Cholesterol, triglycerides	CBC, ESR, CRP, ASAT, ALAT
Rituximab	Chest X-ray, RF (for M05), tuberculin test, hepatitis markers CBC, ASAT, ALAT	CBC, ESR, CRP, ASAT, ALAT

*Apply certified copies of the original forms (if hospitalization up to one month prior to the application a copy of their medical records with the number is applied)

**Up to the 6th month controlled once a month, after the 6th month - when applying for continuing treatment (new protocol)

Requirements of the NHIF in the treatment of seropositive rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, and ankylosing spondylitis with biologic anti-rheumatic drugs in patients >18 years in outpatient care, 15 March 2013

Biologic Market in Bulgaria

- Biologic market in Bulgaria*:
  - 9,9 million EUR in 2012 , vs. 5,7 in 2011 and 2,3 in 2010
  - 73,5% growth vs. 2011
- Available products:
  - Anti-TNF's: etanercept (Enbrel), adalimumab (Humira), certolizumab pegol (Cimzia), infliximab (Remicade), golimumab (Simponi), since 15 March - tocilizumab (RoActemra) and rituximab (MabThera) 2013
- Patients treated with anti-TNF's in 2012: 1291
  - 39.3% with RA (507 patients)
  - 44.6% with AS (576 patients)
  - 12.4% with PsA (160 patients)
  - 3.5% with JIA (45 patients)
  - 0.3% others (3 patients)

*Source: IMS Health; L4B Anti-TNF Products

Biologic Market in Bulgaria

- Despite the increased utilization of biologic agents in the treatment of inflammatory joint diseases in Bulgaria, the proportion of their users is too small, compare to other EU countries.
  - This indicates that the access to expensive and highly effective treatments with biologic DMARDs is very limited in Bulgaria
- The reimbursement policy of the health insurance system is the key to improving the access to biologic agent treatment

Cost analysis of the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis with synthetic and biologic disease modifying antirheumatic drugs for 2010 in Bulgaria, Rheumatology, 19, 2011, №4, 59-67.

Market access limitations

- Access to rheumatologists and early diagnosis and treatment
- 1 rheumatologist for 60000 of the population over 18 years
- unevenly developed rheumatology network
- improper reffereing of rheumatic patients by GP's to other specialists (orthopedists, neurologists, physiotherapists)
- There are ~100 rheumatologists in Bulgaria.
- Too much documentation

Cost analysis of the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis with synthetic and biologic disease modifying antirheumatic drugs for 2010 in Bulgaria, Rheumatology, 19, 2011, №4, 59-67.

Monitoring/continuation and switches of biologic agents

- Evaluation of therapeutic effect and safety profile is carried out at the end of the 3rd, 6th and 12th month of treatment.
- Tracking of clinical and laboratory parameters, disease activity, HAQ. The effect on X-ray changes is evaluated after one year of treatment
- Biologic agents have to be stopped in case of lack of therapeutic response or occurrence of intolerance
- At each visit, patients are monitored for adverse events. Further terapeutic approch is determined by the type and severity of adverse events occurred

National consensus for treatment of rheumatoid arthritis with biologic agents, September 2008

Initiation of treatment with TNF-inhibitor

- Before starting treatment with TNF-inhibitor:
- Detailed history
- Physical examination
- Complete articular status
- Duration of morning stiffness, intensity of pain (100 mm VAS), TJC, SJC
- Global assessment of disease activity by physician and by patient (100 mm VAS)
- DAS-28, HAQ
- X-ray of affected from RA joints
- Assess the need an ultrasound of internal organs
- It is recommended during treatment to monitor ACR20, 50 and 70

National consensus for treatment of rheumatoid arthritis with biologic agents, September 2008

Initiation of treatment with TNF-inhibitor

- Before starting treatment with TNF-inhibitor

- Laboratory test: complete blood count, ESR, fibrinogen, CRP, RF, anti-CCP antibodies, liver enzimes, alkaline phosphatase, bilirubin, total serum protein, albumin, creatinine, blood sugar, urine – general test
- Mandatory: for active and latent TB (history, status, skin test, chest X-ray).

In active TB – no treatment with anti-TNF. In latent TB – 9 months preventive treatment with Isoniazid, which allows treatment with anti-TNF. Screening for TBC-PPD or Quantiferon.

- Other laboratory parameters and examination are possible

National consensus for treatment of rheumatoid arthritis with biologic agents, September 2008

TB screening, TB profilaxis, Hepatitis screening

- In Bulgaria TB screening is conducted through the usage of PPD-skin test, QuantiFERON-TB Gold Test. TB screening is compulsory before the start of therapy with a biological agent and once year afterwards.
- Another obligatory condition for treatment with a biological agent is prior screening for Hepatitis B and C.
- When there is evidence for the presence of active or latent Tubercolosis, treatment is administered for 6 months with triple anti-TB therapy.

Local Guidelines

- National consensus for treatment of rheumatoid arthritis with biologic agents, September 2008

Local Journal

- “RHEUMATOLOGY”, 4 issues per year

Local Society

- Bulgarian Society for Rheumatology

http://www.rheumatologybg.org/

Local patient organizations

- Association of patients with rheumatoid arthritis (APRA)

http://www.apra-bg.org/

- Bulgarian association of patients with Ankylosing Spondylitis

http://bg.spondylitisbg.org/

- Organization of patients with rheumatic diseases in Bulgaria (OPRDB)

http://blog.revmatologia.org/

Thank you for your attention!