® Postepy Hig Med Dosw (online), 2016; 70: 896-900
e-ISSN 1732-2693

www.phmd.pl
Original Article

Received: 2016.05.25
Accepted: 2016.08.01
Published: 2016.09.01

Frequency of the use of biological treatment of patients with rheumatoid arthritis and ankylosing spondylitis in Lower Silesia

Częstość stosowania leczenia biologicznego na Dolnym Śląsku u chorych z reumatoidalnym zapaleniem stawów i zesztywniającym zapaleniem stawów kręgosłupa

Wojciech Tański[1, A, B, C, D, E, F], **Angelika Chachaj**[1,2, B, C, D, E, F], **Katarzyna Drożdż**[1,2, D, E, F], **Andrzej Szuba**[1,2, A, D, E]

[1]Department of Internal Medicine, 4th Military Hospital in Wroclaw
[2]Division of Angiology, Wroclaw Medical University

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic connective tissue diseases. Inadequate treatment of RA and AS results in health failure, disability and premature death. In recent years, development of immunology and genetic engineering techniques has started a new generation of drugs in the treatment of RA and AS, called biologic response modifiers or biologics. It is a very effective therapy of serious RA and AS. In many cases, they represent the only way to improve the quality of life, slowing or even arresting the development of these diseases. According to national statistics, the percentage of patients with rheumatic diseases treated with biologic treatment in Poland is less than 1.5%, and it is much lower than in Western European countries (20%).

Purpose: The aim of the study was to evaluate the use of biological treatment in Lower Silesia in patients with RA and AS in the years 2006-2015, based on data obtained from the Lower Silesian Branch of the Polish National Health Fund.

Results: In the last 10 years the frequency of biological treatment of RA or AS in Lower Silesia was estimated as 2.06% of patients (in 2011) to 6.03% of patients (during the first 8 months of 2015). Biological treatment is more often used in Lower Silesia in comparison to national statistics and ranks at a similar level as in other countries of Central and Eastern Europe.

Key words: rheumatoid arthritis • ankylosing spondylitis • biological treatment

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID= 1216375

Word count: 2215
Tables: 1
Figures: –
References: 17

Author's address: Andrzej Szuba, MD PhD Professor of Medicine Division of Angiology, Wroclaw Medical University and Department of Internal Medicine, 4th Military Hospital in Wroclaw, Weigla 5 street; 50- 981 Wroclaw, Poland phone/fax: +48 261 660599 mobile: +48 504 085 101 email: szubaa@yahoo.com; andrzej.szuba@umed.wroc.pl

Abbreviations: **AS** – ankylosing spondylitis, **bDMARD** – biological disease-modifying antirheumatic drug, **csDMARD** – conventional synthetic disease-modifying antirheumatic drug, **GKS** – glucocorticoids, **JIA** – juvenile idiopathic arthritis, **NSAIDs** – non-steroidal anti-inflammatory drugs, **PsA** – psoriatic arthritis, **RA –** rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are chronic inflammatory connective tissue diseases primarily affecting joints. Due to their progressive nature they lead to destruction of joints, their deformation and finally to disability and premature death [10,11].

The prevalence of RA and AS was estimated respectively at 0.5-1.1% and 0.24% in the European populations [1,3,15].

Early diagnosis and concomitant start of the treatment are fundamental to improving the outcome of patients. The aim of the treatment in these diseases is rapid and sustainable reduction of the inflammatory process. Effective management in the first period of these diseases plays a pivotal role in improving the long-term prognosis by preventing severe joint destruction and disability (called the "therapeutic window of opportunity"). In RA the first two years of the disease have the greatest impact on the further prognosis. Appropriate treatment should be implemented at the time of diagnosis of RA and AS, especially in patients with risk factors for poor prognosis, such as high disease activity, presence of autoantibodies and early joint damage [10,11].

In Poland, according to the guidelines of EULAR 2013 (The European League Against Rheumatism), RA treatment begins with the application of conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy, such as methotrexate, leflunomide and sulfasalazine. They possibly may be used in combination with low-dose glucocorticoids (GKS) [12].

The first-line drugs for AS treatment are non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors. In patients with peripheral disease corticosteroid injections directed to the local site of musculoskeletal inflammation may also be considered. However, there has been no evidence for the efficacy of csDMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease. Sulfasalazine may be effective only in patients with peripheral arthritis [2,17]. Lack of efficacy of csDMARDs in patients with AS causes that patients may be deprived of the possibility of effective treatment for a long time.

In recent years, the development of immunological and genetic engineering techniques has started a new generation of drugs in the treatment of RA and AS, called biological disease-modifying antirheumatic drugs (bDMARDs). These drugs block the key inflammatory cytokines in the pathogenesis of RA and AS, i.e. TNF-α (adalimumab, certolizumab, etanercept, golimumab, infliximab), IL-1β (anakinra), and IL-6 (tocilizumab). Abatacept and rituximab are the other bDMARDs used in the treatment of RA. They block respectively CD28 antigen on the surface of T lymphocytes and CD20 antigen on the surface of B lymphocytes [11].

The bDMARDs are new drugs that allow one to control the course of serious RA and AS in many patients. Therefore, they represent a significant breakthrough in the management of these diseases.

Guidance on the recommendations of the use of bDMARDs in the treatment of RA and AS vary considerably from country to country. Originally, they are created by a group of experts in the field of rheumatology, and then, due to the high cost of treatment, are modified by the national health funds. In Poland, in comparison to other European countries, access to biological therapy is significantly limited.

According to the recommendations of the guidelines of EULAR 2013, the use of bDMARDs in RA should be implemented only when the treatment goal is not achieved by the use of csDMARDs for 6 months, provided that the treatment should be modified or changed if there is no evidence of improvement at 3 months *after the start of treatment [12].*

According to the consensus statement of the Assessment of SpondyloArthritis International Society (ASAS 2010), biologic treatment of AS may be applied in the case of ineffectiveness of a minimum of two different NSAIDs in maximum recommended or tolerated doses for a minimum of 4 weeks in total. Patients with peripheral symptoms should also have had an ineffective treatment with sulfasalazine and at least one intraarticular injection with GKS [2,17].

Currently, the biologic therapy in rheumatic diseases in Poland is applied in the following therapeutic programs of the National Health Fund:

- treatment of RA and aggressive course of juvenile idiopathic arthritis (JIA);
- treatment of aggressive course of psoriatic arthritis (PsA);
- treatment of severe, active AS with inhibitors of TNF alpha;
- treatment of aggressive course of RA [5].

Despite clear EULAR 2013 recommendations concerning qualification for therapy with biologic drugs, the proportion of RA patients receiving biological treatment in Poland in 2009 and in 2012 was below 1.5%. Among other countries of Central and Eastern Europe the percentage of patients receiving biological treatment in 2009 was higher: in Hungary 5% of patients with RA were treated biologically, in Slovenia 4.5%, in Slovakia –3.5%, in the Czech Republic 2.92%, in Romania 2.2%, and in Estonia 1.8% [7,14]. At the opposite extreme are Germany, Sweden and England. Biological treatment in these countries in 2012 was received by up to 20% of patients with RA, and in Norway 30% of patients with RA, which means that access to biological anti-RA drugs is available to everyone whose disease activity requires its use [14].

Apart from joints, RA may also be associated with extraarticular manifestations, ranging in different countries from 12.9 to 35.6%. These extraarticular symptoms include cardiovascular disease, generalized osteoporosis, lymphadenopathy, pleurisy, vasculitis and Felty's syndrome [16]. It has been shown that the frequency of extraarticular manifestations varies widely across Europe and is in the range of 12.9% to 35.6%. Poland, Germany, Denmark and the UK are the countries of the highest prevalence of systemic symptoms affecting distant organs. In Poland the prevalence of extraarticular RA was estimated at 33.5%. The lowest prevalence of extraarticular disease was observed in the Netherlands and in Italy (at the level of 13%) [6,13]. Extraarticular symptoms are associated with a worse prognosis and are a strong argument for the use of biological treatment [16].

In Poland, the qualification of patients for application of biological treatment in RA and AS is done at the request of a rheumatologist by the Team Coordinating the Biological Treatment of Rheumatic Diseases, that is appointed by the President of the Polish National Health Fund. Information about the number of patients receiving biological treatment is available in the reports of the Team Coordinating the Biological Treatment of Rheumatic Diseases and published on the websites of the Polish National Health Fund [8].

According to the data available on the websites of the Polish National Health Fund in January 2011, the number of patients who received at least the first dose of biological drug was 2577 (with RA – 1573, with JIA – 344, with AS – 660). In July 2015 the number of patients actively treated with biological agents was 5985. In all the therapeutic programs of the National Health Fund, biological treatment was applied to 10 014 patients (with RA – 5440, with JIA – 986, with AS – 2476, with PsA – 1112). Analysis reports for 2015 showed that the average number of patients newly included in the therapeutic program was estimated at about 100 people per month [8].

The aim of this study was to evaluate the frequency of biological treatment in patients with RA and AS during the last 10 years in Lower Silesia.

Material and methods

The analysis was based on the register received from the Lower Silesian Branch of the Polish National Health Fund. This register contained data concerning the following:

- the number of patients treated within the Lower Silesian Branch of the Polish National Health Fund because of RA or AS in each year of the period from 2006 to 2015;
- the number of patients with RA or AS receiving bDMARDs in each year of the period from 2006 to 2015 within the therapeutic programs funded by the Lower Silesian Branch of the Polish National Health Fund.

Based on these data, the percentage of patients with RA or AS who received bDMARDs in each year of the period from 2006 to 2015 within the therapeutic programs funded by the Lower Silesian Branch of the Polish National Health Fund was calculated.

Results

The quantity and the percentage of the number of patients with RA or AS who received bDMARDs in each year of the period from 2006 to 2015 within the therapeutic programs funded by the Lower Silesian Branch of the Polish National Health Fund are presented in Table 1.

Discussion

In the last 10 years, biological treatment of RA or AS in Lower Silesia was applied to 2.06% of patients in 2011, increasing to 6.03% of patients in the first eight months of 2015. The application of biologic therapy in Lower Silesian patients with RA or AS was more frequent than average in Poland. According to the national statistics, less than 1.5% of patients with rheumatic diseases in Poland receive biologic agents [14]. The frequency of biologic therapy in Lower Silesia ranks at a similar level as in other countries of Central and Eastern Europe.

This result may be partly explained by the easier access to rheumatology clinics in the Lower Silesia region compared to other parts of the country [14].

According to the Polish report published in 2011, over 50% of the rheumatology clinics were located in four

Table 1. Number of patients with RA or AS receiving bDMARD in the Lower Silesian Branch of the National Health Fund during the last 10 years

Year	Number of patients treated in the Lower Silesian Branch of National Health Fund because of RA or AS	Number of patients with RA or AS receiving bDMARD in the therapeutic programs in the Lower Silesian Branch of National Health Fund	The number of new patients with RA or AS, starting biological treatment in the therapeutic programs in the Lower Silesian Branch of National Health Fund in a given year
2006	8 695	179 (2.06 %)	–
2007	8 828	206 (2.33 %)	66
2008	9 261	305 (3.29 %)	132
2009	9 656	416 (4.31 %)	160
2010	9 180	477 (5.20 %)	138
2011	9 015	336 (3.73 %)	102
2012	10 175	407 (4.00 %)	118
2013	10 305	478 (4.64 %)	125
2014	10 856	529 (4.87 %)	104
2015 (from January to August)	9 135	551 (6.03 %)	106

provinces – Mazovia, Silesia, Lower Silesia and Malopolska. The number of inhabitants per rheumatologist showed a similar pattern: half of practicing rheumatologists in 2011 had registered medical practices in four provinces: Mazowsze, Silesia, Lower Silesia and Malopolska. In these provinces the indicator of the amount of inhabitants per rheumatological clinic ranged from 12 000 to 15 000. The fewest rheumatology clinics were noted in the provinces of Opole, Lubuskie, Warmia-Mazury and Podlasie. In these provinces the number of inhabitants per rheumatological clinic was over 30 000 [4,9].

There have been published several reports on issues related to biological treatment in rheumatic diseases in Poland in recent years [4,9,17]. They all clearly indicate a major limitation for patients with rheumatic diseases in the availability of biological treatment in Poland.

The production costs of biological agents using recombinant DNA technology are very high. Clinical tests, technological expenses and extended production time raise the price to a level not available to most patients. However, reducing the financial calculation of application of biological agents to the price of the therapy is oversimplification. The issue seems no longer so evident when we increase the calculation by social expenditure, pensions, depletion of budgetary revenues resulting from absenteeism of employees and their ultimate exclusion from the labor market, and finally the development of other diseases and degradation of the individual [14]. Healthcare contends with a lack of financial resources every day and at any location, but the underfunding in the segment of biological drugs is especially explicit.

Biological therapies are very effective treatment of serious RA and AS and in many patients represent the only way to improve the quality of life, arresting or slowing disease progression. Meanwhile, the Polish Health Ministry restricted the use of biological drugs to therapeutic programs in accordance with an administrative interpretation. Therapeutic programs in Poland seem to be a bureaucratic instrument of control and pressure, blocking the ability to implement the right treatment process, which should be the result of the doctor's decision, based on current medical knowledge – such conclusions were drawn after thorough analysis in a report by Lazarski University [9].

According to current regulations that define participation in the drug programs, the expected response to the biologics are closely described in each program and evaluated, among other things, on the basis of the DAS 28. However, not every patient responds to the treatment at checkpoints at the proper rate and meets the requirements of the program. This is often the reason for the discontinuation of the treatment, despite observed benefits (reduction of pain, improved quality of life). This scheme forecloses the individual approach to biologic therapy. Additionally, the physician is limited in his selection to the drugs listed in the program, instead of a broader base of drugs registered in the country and with appropriate indications. The requirement for the completion of biological therapy in case of low disease activity over a period of 18 months is a crowning touch to this policy. Only the next relapse of disease re-enables the subsequent qualification procedure for biologic treatment. Unfortunately, the effectiveness of the drug at the next disease exacerbation is often lower. The moment of withdrawal of the biological treatment in people with achieved low disease activity is still a subject of debate. The treatment endpoint required by the current program results in a high relapse rate of disease [4,9].

The present study has some limitations, resulting from not taking into account the patients treated biologically in randomized clinical trials and patients using only private sector medical services.

It seems that patients who bear the full costs of biological treatment in Poland constitute a small percentage, unlike the patients participating in randomized clinical trials. According to data obtained by patient organizations from the Central Register of Clinical Trials, the currently ongoing clinical trials in Poland are already treating a larger group of patients compared to the group treated with active therapeutic programs. The clinical trials in Poland significantly substitute the biologic therapy of rheumatic diseases [4].

Treatment of patients in randomized clinical trials is for the payer attractive as the costs associated with the diagnosis and treatment are borne by the company, which orders the data study. However, in this arrangement, the patient is not sure whether the drug is replaced by placebo [4].

The authors have no potential conflicts of interest to declare.

References

[1] Alamanos Y., Drosos A.A.: Epidemiology of adult rheumatoid arthritis. Autoimmun. Rev., 2005; 4: 130-136

[2] Braun J., van den Berg R., Baraliakos X., Boehm H., Burgos-Vargas R., Collantes-Estevez E., Dagfinrud H., Dijkmans B., Dougados M., Emery P., Geher P., Hammoudeh M., Inman R.D., Jongkees M., Khan M.A., et al.: 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann. Rheum. Dis., 2011; 70: 896-904

[3] Dean L.E., Jones G.T., MacDonald A.G., Downham C., Sturrock R.D., Macfarlane G.J.: Global prevalence of ankylosing spondylitis. Rheumatology, 2014; 53: 650-657

[4] JA PACJENT! Perspektywa Organizacji Pacjenckich na Stan Opieki Reumatologicznej w Polsce RAPORT 2014. http://zzsk.org.pl/documents/JaPacjentRaportStanuReumatologii2014.pdf (20.05.2016)

[5] Ministerstwo Zdrowia. Programy lekowe. http://www.mz.gov.pl/leki/refundacja/programy-lekowe (20.05.2016)

[6] Naranjo A., Sokka T., Descalzo M.A., Calvo-Alén J., Horslev-Petersen K., Luukkainen R.K., Combe B., Burmester G.R., Devlin J., Ferraccioli G., Morelli A., Hoekstra M., Majdan M., Sadkiewicz S., Belmonte M., et al.: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res. Ther., 2008; 10: R30

[7] Orlewska E., Ancuta I., Anic B., Codrenau C., Damjanov N., Djukic P., Ionescu R., Marinchev L., Nasonov E.L., Peets T., Praprotnik S., Rashkov R., Skoupa J., Tlustochowicz W., Tlustochowicz M., et al.: Access to biologic treatment for rheumatoid arthritis in Central and Eastern European (CEE) countries. Med. Sci. Monit., 2011; 17: SR1-SR13

[8] Protokoły z posiedzeń Zespołu Koordynacyjnego ds. Leczenia Biologicznego w Chorobach Reumatycznych (od początku 2011 r.). http://www.nfz.gov.pl/dla-swiadczeniodawcy/zespoly-koordynujace/reumatologia-protokoly-z-posiedzen. (20.05.2016)

[9] Raport Uczelni Łazarskiego – Stan opieki reumatologicznej w Polsce 2015

[10] Raychaudhuri S.P., Deodhar A.: The classification and diagnostic criteria of ankylosing spondylitis. J. Autoimmun., 2014; 48-49: 128-133

[11] Smolen J.S., Aletaha D., McInnes I.B.: Rheumatoid arthritis. Lancet, 2016 (in print)

[12] Smolen J.S., Breedveld F.C., Burmester G.R., Bykerk V., Dougados M., Emery P., Kvien T.K., Navarro-Compán M.V., Oliver S., Schoels M., Scholte-Voshaar M., Stamm T., Stoffer M., Takeuchi T., Aletaha D., et al.: Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann. Rheum. Dis., 2016; 75: 3-15

[13] Sokka T., Kautiainen H., Toloza S., Makinen H., Verstappen S.M., Lund Hetland M., Naranjo A., Baecklund E., Herborn G., Rau R., Cazzato M., Gossec L., Skakic V., Gogus F., Sierakowski S. et al.: QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann. Rheum. Dis., 2007; 66: 1491-1496

[14] Stajszczyk M.: 2013. Raport Leczenie biologiczne w chorobach reumatycznych. https://issuu.com/jackrobat/docs/zmiany_raport_a4_wersja_elektronicz (20.05.2016)

[15] Tobón G.J., Youinou P., Saraux A.: The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. J. Autoimmun., 2010; 35: 10-14

[16] Turesson C., Jacobsson L., Bergström U.: Extra-articular rheumatoid arthritis: prevalence and mortality. Rheumatology, 1999; 38: 668-674

[17] van der Heijde D., Sieper J., Maksymowych W.P., Dougados M., Burgos-Vargas R., Landewe R., Rudwaleit M., Braun J.: 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann. Rheum. Dis., 2011; 70: 905-908

The authors have no potential conflicts of interest to declare.