FARMACIA, 2019, Vol. 67, 4

https://doi.org/10.31925/farmacia.2019.4.25

ORIGINAL ARTICLE

EVALUATION OF REIMBURSEMENT POLICY ABOUT ANTI-TNF AGENTS IN TURKEY

EMRAH BILGENER *

Nursing Department, Faculty of Health Sciences, Hitit University, Çorum, Turkey

**corresponding author: emrahbilgener@hitit.edu.tr*

Manuscript received: November 2018

Abstract

Anti-TNF (anti-tumour necrosis factor) agents are currently used in many rheumatic diseases. This research aims mainly to evaluate the reimbursement policy about anti-TNF drugs in Turkey. The analysis has been carried out according to the anti-TNF reimbursement rules with the consumption data for the years 2012 - 2017. The cost tables have been prepared with the reimbursement prices and the medication prospectus doses approved by Turkish Ministry of Health. The results of the research indicate that anti-TNF agents have different treatment costs and adalimumab offers the lowest 12-month treatment costs for the diseases mentioned in the study. For a fair, obtainable and sustainable medication policy, Social Security Administration (SSA) has to reimburse the other molecules from the 12-month treatment cost of adalimumab. The current policies are far from being pharmacoeconomic and if this continues the resources will not be used in an efficient way for public health in Turkey.

Rezumat

Agenții terapeutici anti-TNF (factor de necroză tumorală) sunt utilizați în prezent în multe patologii reumatice. Acest studiu vizează în principal evaluarea politicii de rambursare privind medicamentele anti-TNF din Turcia. Analiza a fost efectuată în conformitate cu regulile de rambursare anti-TNF, corelate cu datele privind consumul pentru anii 2012 - 2017. Tabelele de costuri au fost elaborate cu prețurile de rambursare și cu dozele din prospect aprobate de Ministerul Sănătății din Turcia. Rezultatele cercetării indică faptul că agenții anti-TNF au costuri diferite de tratament, iar adalimumabul oferă cele mai mici costuri pe 12 luni pentru bolile menționate în studiu. Pentru o politică echitabilă, accesibilă și durabilă, Administrația de Securitate Socială (SSA) trebuie să ramburseze celelalte molecule din costul tratamentului cu adalimumab pe 12 luni. Politicile actuale sunt departe de a fi farmacoeconomice și dacă acest lucru va fi perpetuat, resursele nu vor fi utilizate într-un mod eficient pentru sănătatea publică din Turcia.

Keywords: anti-TNF agents, cost analysis, pharmacoeconomics, Turkish health system

Introduction

Anti-TNF agents improve the symptoms and signs of rheumatoid arthritis (RA); they suppress the progress of structural damage and correct physical function [9]. In rheumatoid arthritis treatment, the improving effect of anti-TNF agents starts faster than disease modifying anti-rheumatic drugs (DMARDs). Anti-TNF agents are more effective when are combined with methotrexate in RA [13]. It is pointed out that their effects are equivalent in performed controlled clinical trials. Such factors like the dose and method of usage affect the selection of the drug [9]. In literature, it is possible to find various studies on anti-TNF agents. Nixon *et al*. [22] compared the effects of anti-TNF agents in 13 publications and Singh *et al*. [27] compared it from 27 clinical trials. None of these studies have included the head-to-head comparisons. In many different meta-analyses published in recent years, it was found that these drugs are difficult to rank in RA [7]. The data of the head-to-head clinical trials directly comparing biologic agents are not enough in RA treatment [1, 20]. Over a decade of observational studies and the patient databases report that these agents are effective and reliable in RA treatment [12, 17]. Approximately 30% of the patients in the therapy of RA are discontinued anti-TNF treatment due to unresponsiveness and undesirable side effects [3]. In the GO-AFTER study, it has been shown that another anti-TNF agent may be effective in the patients who have previously been on medication with anti-TNF agent [11].

Table I

Indications of anti-TNF agents for rheumatologic diseases use on [23]

Rheumatoid arthritis and early rheumatoid arthritis
Ankylosing spondylitis
Psoriasis and psoriatic arthritis
Juvenile idiopathic arthritis
Granulomatous diseases (Crohn, sarcoidosis etc.)
Behcet's disease
Others

Ankylosing Spondylitis (AS) displays main effects in sacroiliac joints and vertebral colon. This chronic

inflammatory disease has symptoms such as bowel involvement and uveitis; it also affects large joints and tendon-bones [9]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first options for the treatment [29]. Approximately 20% of the patients with AS have resistance to NSAIDs. Some patients cannot use NSAIDs because of the side effects in the gastrointestinal system. The effects of DMARDs, such as sulfasalazine and methotrexate could not be ankylosing spondylitis [2]. The effects of anti-TNF agents on AS have been demonstrated by long-term studies [9]. According to Norwegian database, the rate of 1-year anti-TNF agent attendance is 78% in AS and 65% in RA [10]. Anti-TNF agents are prescribed for the patients with AS who still have active disease despite of the conventional treatment. While improving the clinical signs and the symptoms, in AS, they also improve the physical functioning and the quality of life [16]. The clinical effects do not change in the long-term usage. When the treatment with them is stopped, the symptoms return back within 6 - 18 weeks. The drugs are effective again with the repetition of the treatment. Also at the treatment of AS like RA, there is no study showing the superiority of anti-TNF agents against each other [5, 9]. Future studies should pay more attention to the comparison of anti-TNF agents with each other, rather than being compared to placebo [20, 25, 30].

Approximately 20% of the patients with psoriasis have arthritis, occurring deformity in peripheral joints and spine. Psoriasis's burden and labour loss are similar to RA and AS [32]. DMARDs such as methotrexate and cyclosporine are used in the therapy of psoriatic arthritis. The effects and safety of anti-TNF inhibitors in psoriasis arthritis (PsA) have been shown in various studies and these groups of agents have suppressed the joint findings more rapidly and significantly than DMARDs and placebo [5, 9]. Their clinical effects start quickly and last long. This group of medications affect the quality of life positively and the rate of continuation of treatment is high. There are no studies directly comparing the effects of anti-TNF drugs on PsA. The studies have shown that the clinical effects are equivalent [9]. Future studies are urgently needed for directly comparing different biological agents and assessing the efficacy of treatment strategies specific for PsA [5].

The risk of severe infection (bacterial, viral, fungal) occurrence in the patients using anti-TNF was found to be 1 to 3 times higher than the patients using DMARDs [6, 19]. The risk of new tuberculosis infection and the risk of latent tuberculosis reactivation have been reported to increase 2-fold in the patients taking anti-TNF agents compared to patients with RA using DMARDs. This risk of infection increases in the patients using anti-TNF along with steroids [8, 24, 28]. The patients with active and latent tuberculosis have to be examined before starting the treatment with them [9, 26].

RA, AS and PsA are the most common inflammatory rheumatic diseases [21]. Biological therapies offer unique advances in the disease activity, the quality of life and the radiological findings [31]. Observational studies indicate that they have similar activities and they are cost-effective comparing to the conventional drugs [5, 9, 20, 25, 27, 30, 31]. But, there is lack of evidence directly comparing the effectiveness of the drugs against each other [20]. There are no evidence-based strategies currently available for guiding to prescribe biological agents [5]. There are few studies about rheumatic diseases burden [18, 32]. They have remarkable side effects such as infection that are worth to consider [6, 8, 9, 19, 24, 26, 28]. Future research should include head-to-head trials comparing the clinical effectiveness and the cost-effectiveness of the medications against each other [20]. It is impossible to directly compare the incremental cost-effectiveness ratios (ICERs) of studies because of the different approaches to modelling (in particular time horizon, country of origin, perspective chosen, prices, etc.) [15].

The medication reimbursement prices and licenses are determined by the Ministry of Health in Turkey. But the reimbursement rules are determined by Social Security Administration (SSA) with yearly declared "Communiqué on Healthcare Practices" (SUT). Article 4.2.1.C-1 of the SUT describes the conditions for anti-TNF drugs [4].

According to the Article 4.2.1.C-1 of SUT, for the adult patients with RA, "If at least three different DMARDs, one being methotrexate, have been used for at least each of the three months (with DAS score greater than 5.1) and the disease activity cannot be controlled though, then the treatment can start based on the three-month medical board report. If the DAS score falls more than 0.6 points (1.2 pts for certolizumab) in the evaluation made 3 months after the beginning of the treatment, this is continued for 3 months (6 months for certolizumab), provided that this is stated in the additional 3-month (6 months for certolizumab) medical board report. If the DAS 28 score decreases by more than 1.2 points at the end of this report, the treatment can be continued provided that his is stated in the additional 6-months medical board report. During the treatment, DAS 28 criteria are reviewed every 6 months and the initial and new DAS 28 scores are indicated in each health board report. If the DAS 28 score does not decrease more than 1.2 points contrasting to the initial one, then the treatment is terminated" [4].

SSA determined the reimbursement rules for anti-TNF drugs in RA according to the changes in disease activity scores (DAS 28) without combined treatments or direct and indirect costs.

In the same article, it is stated that for patients with AS with axial involvement and also for patients with axial spondyloarthritis without evidence of AS, treatment

can be started for 3 months when the response is not enough, even if at least 3 nonsteroidal anti-inflammatory drugs, one of which is the maximum dose of indomethacin, is used at the maximum dose and also in spite of the cases where erythrocyte sedimentation rate > 28 mm/s, or CRP value exceeding the upper limit of normal or active sakroilitis/spondylitis indicated by MR/scintigraphy. If BASDAI score drops more than 2 points after 3 months, the treatment is continued for another 6 months. If the BASDAI score does not decrease more than 2 points contrasting to the initial one, then the treatment is terminated [4]. In this sense the reimbursement rules for anti-TNF agents in AS is based on the disease healing score.

Correspondingly in the same article for PsA; "If at least three different DMARDs have been used for at least three months each (have at least three sensitive joints and at least three swollen joints in two separate examinations performed one month apart) and the disease activity cannot be controlled though, then the treatment can start based on the three-month medical board report. The efficacy of the drug will be evaluated 3 months after starting the treatment. If there is a response at PSARC score, the treatment is continued for another 6 months. Otherwise, the treatment is terminated" [4]. Regarding the treatment of PsA, reimbursement is made according to the changes in PSARC scores.

It is understood that the regulations put down by SSA do not include any rules for anti-TNF agents based on the pharmacoepidemiological data or direct and indirect costs (such as cost of infusion and injection, combined treatments and the secondary treatment costs, the quality of life, the healthcare time and the costs, etc.). It is realized that SSA acknowledges these agents with the similar activity, implementation method and efficiency for the treatments.

Materials and Methods

In this analysis, comparative studies conducted after 2005 about anti-TNF agents were screened in PubMed, Scopus and Ebsco indices. There is lack of evidence directly comparing the effectiveness, safety and the costs of the drugs. The limitations of the study are inadequacy of evidence for assessing the clinical data of anti-TNF agents and the absence of head-to-head trials comparing the medications. In literature, all observational studies have been performed with placebo, NSAID and DMARD medications. The consumption of unit market and the cost data have been obtained from IMS/health-Turkey for the years 2012 - 2017. The reimbursement rules about anti-TNF agents at "Communiqué on Healthcare Practices" (SUT) were investigated. In order to evaluate the reimbursement policy of anti-TNF agents in Turkey, the analysis has been conducted with reimbursement prices according to the approved prospectus usage doses.

Results and Discussion

The starting dose of medication should have achieved the expected regression in the disease scores. Then treatment is continued for maintenance. The starting and maintenance treatment doses approved by the Ministry of Health are given in Table II.

Table II

Approved starting and maintenance treatment doses of anti-TNF agents

medication	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis
adalimumab	40 mg every 2 weeks. Maintenance dosage is 40 mg *per* every 2 weeks	40 mg every 2 weeks. Maintenance dosage is 40 mg *per* every 2 weeks	40 mg every 2 weeks. Maintenance dosage is 40 mg *per* every 2 weeks
etanercept	50 mg every week. Maintenance dosage is 50 mg *per* every weeks	50 mg every week. Maintenance dosage is 50 mg *per* every weeks	50 mg every week. Maintenance dosage is 50 mg *per* every weeks
infliximab	3 mg/kg at 0, 2 and 6 weeks. Maintenance dosage is 3 mg/kg *per* every 8 weeks	5 mg/kg at 0, 2 and 6 weeks. Maintenance dosage is 5 mg/kg *per* every 6 or 8 weeks	5 mg/kg at 0, 2 and 6 weeks. Maintenance dosage is 5 mg/kg *per* every 6 or 8 weeks
golimumab	50 mg every 4 weeks. Maintenance dosage is 50 mg *per* every 4 weeks	50 mg every 4 weeks. Maintenance dosage is 50 mg *per* every 4 weeks	50 mg every 4 weeks. Maintenance dosage is 50 mg *per* every 4 weeks
certolizumab pegol	400 mg at 0, 2 and 4 weeks. Maintenance dosage is 200 mg *per* every 2 weeks	400 mg at 0, 2 and 4 weeks. Maintenance dosage is 200 mg *per* every 2 weeks	400 mg at 0, 2 and 4 weeks. Maintenance dosage is 200 mg *per* every 2 weeks

Etanercept realizes the lowest treatment starting cost for three diseases. Certolizumab pegol has the highest treatment starting cost for RA; on the other hand, infliximab has the highest treatment starting cost in AS and PsA (Table III).

The 12-month dosage and treatment costs of anti-TNF agents according to SUT are given in Table IV.

Adalimumab realizes the lowest 12-month treatment cost for 3 diseases. Certolizumab pegol has the highest 12-month treatment cost for RA. For AS and PsA, infliximab in the patients over 80 kg has the highest 12-month treatment cost and in patients under 80 kg certolizumab pegol has the highest cost (Table IV).

Table III

Treatment starting costs (first 3 months) and doses of anti-TNF agents

medication	1 box content and payback price	Rheumatoid arthritis 3-month Dosage and Cost	Ankylosing spondylitis 3-month Dosage and Cost	Psoriatic arthritis 3-month Dosage and Cost
adalimumab	40 mg - 2 units ready to injection 403.80 $	7 dosage (4 boxes) 1,615.55 $	7 dosage (4 boxes) 1,615.55 $	7 dosage (4 boxes) 1,615.55 $
etanersept	50 mg - 2 units ready to injection 198.60 $	12 dosage (6 boxes) 1,191.65 $	12 dosage (6 boxes) 1,191.65 $	12 dosage (6 boxes) 1,191.65 $
infliximab	100 mg - 1 vial for infusion 218.80 $	3 dosage 3 mg/kg (65 - 100 kg 9 boxes) 1,969.12 $	3 dosage 5 mg/kg (60 - 80 kg 12 boxes, 80 kg < 15 boxes*) 2,625.50 $ 3,281.88 $*	3 dosage 5mg/kg (60 - 80 kg 12 boxes, 80 kg < 15 boxes*) 2,625.50 $ 3,281.88 $*
golimumab	50 mg - 1 unit ready to injection 438.00 $	4 dosage (4 boxes) 1,754.15 $	4 dosage (4 boxes) 1,754.15 $	4 dosage (4 boxes) 1,754.15 $
certolizumab pegol	200 mg - 1 unit ready to injection 357.70 $	3 dosage (6 boxes) 2,146.23 $	3 dosage (6 boxes) 2,146.23 $	3 dosage (6 boxes) 2,146.23 $

TL/$: 3.60 (2017)

Table IV

12-month dosages and costs of anti-TNF drugs

medication	RA 12-month dosage and cost	AS 12-month dosage and cost	PA 12-month dosage and cost
adalimumab	24 dosage, 12 boxes 4,846.70 $	24 dosage, 12 boxes 4,846.70 $	24 dosage, 12 boxes 4,846.70 $
etanersept	52 dosage, 26 boxes 5,164.00 $	52 dosage, 26 boxes 5,164.00 $	52 dosage, 26 boxes 5,164.00 $
infliximab	8 dosage (65 kg > 24 boxes, 65 kg < 32 boxes*) 5,251.00 $ 7,001.33 $*	8 dosage (60 kg < 32 boxes, 80 kg < 40 boxes*) 7,001.33 $ 8,751.66 $*	8 dosage (60 kg < 32 boxes, 80 kg < 40 boxes*) 7,001.33 $ 8,751.66 $*
golimumab	13 dosage, 13 boxes 5,694.46 $	13 dosage, 13 boxes 5,694.46 $	13 dosage, 13 boxes 5,694.46 $
certolizumab pegol	21 dosage, 24 boxes 8,584.93 $	21 dosage, 24 boxes 8,584.93 $	21 dosage, 24 boxes 8,584.93 $

TL/$: 3.60 (2017)

In Turkey, the consumption of anti-TNF drugs was reported as 357,126 units in 2012 and 694,634 units in 2017. Within 5 years, the market grew up by approximately 200% (Table V).

SSA paid 126,783,742 $ for anti-TNF agents therapy in 2012. By years, while Turkish Lira losing value against US Dollar, total payment grew up to 138,262,134 $ in 2017 (Table VI)

Table V

Consumption of unit market by years [14]

medication	2012	2013	2014	2015	2016	2017
adalimumab	74,582	91,166	114,002	136,192	156,610	162,849
etanersept	145,853	181,243	190,437	221,100	230,331	232,578
infliximab	137,261	148,107	151,407	173,667	189,590	200,197
golimumab	0	14,215	33,660	45,739	54,229	56,065
certolizumab pegol	0	0	865	14,351	30,309	42,945
Total Market	357,126	434,731	490,371	591,049	661,069	694,634

Table VI

Total costs of anti-TNF agents by years 2012 - 2017 (from the producer price) [14]

	2012	2013	2014	2015	2016	2017
TL/$	1.80	2.00	2.30	2.80	3.20	3.60
Total $	126,783,742	135,999,476	137,300,067	140,401,720	144,95,851	138,262,134
Total TL	228,210,736	271,998,953	315,790,55	393,124,17	462,386,723	497,743,684

Because of the different modelling, perspective and especially prices, it is impossible to make a pharmaco-economic comparison between this study and the others in the literature.

Anti-TNF agents have different dosages (Table II) and the implementation methods (Table III). There are devices ready to use in the boxes of all medications except infliximab (Table III). The patients learn how to use these devices with a short training. However, for the implementation of infliximab, the patients need to stay 8 times in a health facility for 2 - 3 hours each within 12 months (Tables III and IV). This causes indirect costs for the patients and the reimbursement institution. Therefore, it is foreseen that the cost of 12-month treatment of infliximab will be higher than that has been calculated in the study. In the study, etanercept has the lowest treatment starting cost (Table III). However, the treatment maintenance process cost is more important for the reimbursement institutions.

Golimumab, which requires 13 implementations for 12-months treatment, seems to be a suitable choice for patients. On the other hand, adalimumab, which requires 24 implementations and offers the lowest 12-month treatment cost, is considered to be the most suitable choice for the public (Table IV). The most economical treatment should be chosen in order to maintain accessible health services. Approximately 200% increase in the growth of the total market within 5 years is an indication that innovative drugs are accessible to all patients. Social Security Administration has successful policies on the access to innovative therapies. Additionally, the economic resources need to be used in an efficient and controlled manner. According to the observational studies anti-TNF drugs have similar efficacy. In this study, it is seen that adalimumab provides the lowest 12-month treatment cost. But adalimumab is used less than expensive etanercept and infliximab by years. In particular, after the presentations of golimumab and certolizumab to the market, which have higher 12-month treatment costs, their sales have increased in the cumulative terms. It is thought-provoking that higher cost drugs are preferred for the treatment (Table V). While total market grew up, because of the economic situation of Turkey and fixed exchange rate policy of Ministry of Health, the total reimbursement cost did not increase on US dollar terms. However, the total cost in Turkish Lira currency has been increased about 2 times (Table VI).

Conclusions

Anti-TNF drugs have high prices, however, they are cost-effective comparing to the conventional treatments and they have similar effectiveness for the rheumatic diseases. It is predicted that the consumption of them will increase with the new indications in the future. The primary duty of the reimbursement agency is to manage the resources efficiently to provide a fair, quality and sustainable healthcare for the citizens. The economic funds have to be used efficiently to guarantee the financing new and expensive treatments. For this reason, Social Security Administration and Ministry of Health together should make economic analysis with the pharmacoepidemiological data. This study showed the importance of making economic analysis with the pharmacoepidemiological data while setting the reimbursement rules and the prices for similar treatments. Furthermore, analysis showed that adalimumab offers the lowest 12-month treatment cost for Turkey. In order to prevent the wasting of public resources, the medications which commit similar results for the same treatment should not have different and high reimbursement prices.

Therefore; it is considered that for a fair and sustainable reimbursement policy, Social Security Administration should reimburse all the anti-TNF agents from the lowest 12-month treatment cost and Ministry of Health should regulate the medication prices. Otherwise, the current policies are far from being pharmacoeconomic.

References

1. Albert DA, Are all biologics the same? Optimal treatment strategies for patients with early rheumatoid arthritis: Systematic review and indirect pairwise meta-analysis. *J Clin Rheumatol.*, 2015; 21(8): 398-404.
2. Braun J, Sieper J, Ankylosing spondylitis. *Lancet*, 2007; 21,369(9570): 1379-1390.
3. Combe B, Switching between anti-TNF alpha agents: what is the evidence?. *Joint Bone Spine*, 2004; 71(3): 169-171.
4. Communiqué on Healthcare Practices, Sağlık Uygulama Tebliği, Sosyal Güvenlik Kurumu Yayınları, 2018, Ankara, www.resmigazete.gov.tr.
5. D'Angelo S, Tramontano G, Gilio M, Leccese P, Olivieri I, Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders. *Open Access Rheumatol.*, 2017; 9: 21-28.
6. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, Serious infections during anti-TNF alpha treatment in rheumatoid arthritis patients. *Autoimmun Rev.*, 2009; 8(3): 266-273.
7. Fride Tvete I, Natvig B, Gåsemyr J, Meland N, Røine M, Klemp M, Comparing Effects of Biologic Agents in Treating Patients with Rheumatoid Arthritis: A Multiple Treatment Comparison Regression Analysis. *PLoS ONE*, 2016; 11(1): e0146633: 1-17.
8. Furst DE, Keystone EC, Fleischmann R, Mease P, Breedveld FC, Smolen JS, Updated consensus statement on biological agents for the treatment of rheumatic diseases. *Ann Rheum Dis.*, 2013; 72(Suppl 2): 2-34.
9. Hamuryudan V, Uğurlu S, The use of anti-TNF agents in rheumatic diseases. *Turkiye Klinikleri JImmunol Rheumatol-Special Topics*, 2010; 3(2): 9-19.
10. Heiberg MS, Koldingsnes W, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, The comparative one-year performance of anti-tumor necrosis Factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: Results

from a longitudinal, observational, multicentre study. *Arthritis Rheum.*, 2008; 59(2): 234-240.
11. Hyrich KL, Lunt M, Watson KD, Symmons DP, Silman AJ, Outcomes after switching from one anti-tumour necrosis factor alpha agent to a second anti-tumour necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. *Arthritis Rheum.*, 2007; 56(1): 13-20.
12. Hyrich KL, Wat son KD, Isenberg DA, Symmons DP, BSR Biologics Register the British Society for Rheumatology Biologics Register: 6 years on. *Rheumatology (Oxford)*, 2008; 47(10): 1441-1443.
13. Hyrich KL, Deighton C, Watson KD; BSRBR Control Centre Consortium, Symmons DP, Lunt M; British Society for Rheumatology Biologics Register, Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology (Oxford)*, 2009; 48(10): 1323-1327.
14. Iqvia, Turkey Pharmaceutical Index Dataview, IMS/ Health-Turkey 2012 - 2017 Statistics.
15. Joensuu JT, Huoponen S, Aaltonen KJ, Konttinen YT, Nordström D, Blom M, The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: A systematic review. *PLoS ONE*, 2015; 10(3): e0119683: 1-27.
16. Kavanaugh A, Tutuncu Z, Catalan-Sanchez T, Update on anti-tumour necrosis factor therapy in the spondylo arthropathies including psoriatic arthritis. *Ann Rheum Dis.*, 2007; 66(10): 1393-1397.
17. Kristensen LE, Kapetanovic MC, Gülfe A, Söderlin M, Saxne T, Geborek P, Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. *Rheumatology (Oxford)*, 2008; 47(4): 495-499.
18. Kvamme MK, Kristiansen IS, Lie E, Kvien TK, Identification of cut points for acceptable health status and important improvement in patient-reported outcomes, in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol.*, 2010; 37(1): 26-31.
19. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum.*, 2005; 52(11): 3403-3412.
20. Malottki K, Barton P, Tsourapas A, Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis after the Failure of a Tumour Necrosis Factor Inhibitor: A Systematic Review and Economic Evaluation. *Health Tech Asses.*, 2011; 15(14): 1-278.
21. Michelsen B, Fiane R, Diamantopoulos AP, Soldal DM, A Comparison of disease burden in rheumatoid arthritis. psoriatic arthritis and axial spondyloarthritis. *PLoS ONE*, 2015; 10(4): e0123582: 1-11.
22. Nixon RM, Bansback N, Brennan A, Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Stat Med.*, 2007; 26(6): 1237-1254.
23. Pay S, Anti-TNF drug usage in rheumatic diseases. *Turkiye Klinikleri J Med Sci.*, 2006; 26: 430-440.
24. Saliu OY, Sofer C, Stein DS, Schwan der SK, Wallis RS, Tumour-necrosis-factor blockers: differential effects on mycobacterial immunity. *J Infect Dis.*, 2006; 194(4): 486-492.
25. Shu T, Chen GH, Rong L, Feng F, Yang B, Chen R, Wang J, Indirect comparison of anti-TNF-α agents for active ankylosing spondylitis: mixed treatment comparison of randomized controlled trials. *Clin Exp Rheumatol.*, 2013; 31(5): 717-722.
26. Sinem Sağ, Nas K, The use of biological agents in rheumatology. *Online J Turkish Health Sci.*, 2017; 2: 34-45.
27. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ*, 2009; 181(11): 787-796.
28. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO, Granulomatous infectious diseases associated with tumour necrosis factor antagonists. *Clin Infect Dis.*, 2004; 38(9): 1261-1265.
29. Wanders A, Heijde D, Landewé R, Béhier JM, Calin A, Olivieri I, Non-steroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum.*, 2005; 52(6): 1756-1765.
30. Wang Y, Wang H, Jiang J, Zhao D, Liu Y, Comparative Efficacy and Acceptability of Anti-TNF-Alpha Therapy in Ankylosing Spondylitis: A Mixed-Treatments Comparison. *Cell Physiol Biochem.*, 2016; 39: 1679-1694.
31. Wong JB, Cost-Effectiveness of anti-tumour necrosis factor agents. *Clin Exp Rheum.*, 2004; 22(Suppl 35): 65-70.
32. Zink A, Thiele K, Huscher D, Listing J, Sieper J, Krause A, Health care and burden of disease in psoriatic arthritis; A comparison with rheumatoid arthritis and ankylosing spondylitis. *J Rheumat.*, 2006; 33(1): 86-90.