

INFLIXIMAB BIOSIMILAR *VERSUS* METHOTREXATE FOR THE TREATMENT OF MODERATE TO SEVERE PSORIASIS

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Abstract

Psoriasis is a chronic, immune-mediated condition associated with severe impairment in the patient's quality of life. A biosimilar is a biological medicine that is highly similar to another already approved biological medicine and is authorized in accordance with the same standards as all biological treatments. In this study we compared the efficacy of infliximab biosimilar to that of methotrexate in patients with plaque type psoriasis. 16 patients treated with infliximab biosimilar and 30 patients treated with methotrexate were included. The severity of the disease was measured using the Psoriasis Area and Severity Index (PASI) at the beginning of the treatment and then at 3, 6, 9 and 12 months. The primary efficacy endpoint was the proportion of patients achieving an improvement of at least 75% in the PASI (PASI 75). At the end of the study we found that the efficacy of infliximab biosimilar, as measured by PASI 75, was significantly higher than the efficacy of methotrexate and the results were noticed from the very first 3 months of treatment.

Rezumat

Psoriazisul este o afecțiune cronică, mediată imun, asociată cu deteriorarea semnificativă a calității vieții pacienților. Un biosimilar este un tratament biologic foarte asemănător cu un alt tratament biologic deja aprobat care este autorizat în conformitate cu aceleași standarde ca toate tratamentele biologice. În acest studiu am comparat eficiența biosimilarului infliximab cu cea a metotrexatului la pacienții cu psoriazis în plăci. Au fost incluși 16 pacienți tratați cu un medicament biosimilar infliximab și 30 de pacienți tratați cu metotrexat. Severitatea bolii a fost măsurată cu scorul PASI (*Psoriasis Area and Severity Index*) la începutul tratamentului și apoi la 3, 6, 9 și 12 luni. Obiectivul principal a fost identificarea proporției pacienților care au înregistrat o îmbunătățire de minimum 75% a scorului PASI (PASI 75). La sfârșitul studiului am descoperit că eficiența biosimilarului infliximab, măsurată prin PASI 75, este semnificativ mai mare decât eficiența metotrexatului, rezultatele superioare fiind observate încă din primele 3 luni de tratament.

Keywords: Psoriasis, biological therapies, biosimilars, methotrexate

Introduction

Psoriasis is a chronic, immune-mediated polygenic skin disorder with a worldwide occurrence affecting approximately 2% of the population. It is characterized by well demarcated erythematous plaques covered by silvery-white scales symmetrically localized on the extensor aspects of the extremities, especially on the knees, elbows, scalp and lower lumbosacral area [3, 4, 24]. The patient's quality of life is significantly impaired and psychological comorbidities like depression, anxiety and suicidal ideation are common in psoriatic patients [10, 11]. The constant need of treatment represents a real financial burden on both the patient and the healthcare system [1].

Conventional treatment includes topical therapy (corticoids, retinoids, vitamin D analogues,

anthralin, tars) and systemic therapy (methotrexate, acitretin, cyclosporine A), with the latter being employed in severe cases.

Methotrexate is a folic acid analogue that competitively inhibits dihydrofolate reductase (DHFR) and partially inhibits thymidylate synthetase [24]. It was approved in 1971 for the treatment of psoriasis and it is nowadays the first-line systemic treatment for all severe variants of the disease [3]. By inhibiting DHFR, methotrexate inhibits the synthesis of thymidylate and purine nucleotides and therefore DNA synthesis in immunologically active cells. Methotrexate also inhibits 5-aminoimidazole-4-carboxamide ribonucleotide transformylase which increases adenosine tissue concentrations and, therefore, has anti-inflammatory effects [3, 24]. With careful selection

of patients and appropriate monitoring methotrexate is a safe treatment option for patients with plaque type psoriasis [24].

Systemic treatment, including methotrexate, is however frequently associated with adverse reactions (hepatotoxicity, nephrotoxicity, myelosuppression, severe skin reactions, increased risk of malignancy etc.) [3, 24]. Therefore, there is a real need for new alternatives.

Biological therapies in the treatment of psoriasis

Biological therapies are bioengineered molecules that target certain proteins involved in the pathogenesis of immune-mediated disorders. TNF- α blocking agents have proved very effective and safe in the treatment of moderate to severe psoriasis and agents like etanercept, adalimumab and infliximab have been largely used in the last years. Infliximab is a chimeric monoclonal IgG1 antibody which has high specificity, affinity and avidity for TNF- α . It has the advantage of a more rapid onset of action and a higher percentage of patients achieving a 75% reduction in disease activity when compared to other biological treatments and the disadvantage due to its chimeric structure it is associated with the development of anti-drug antibodies [4, 25]. The costs of biologicals are very high and their availability is restricted to the most severely affected patients. As a result, the search for biosimilars began [12].

Biosimilars for the treatment of psoriasis

According to the European Medicine Agency, a biosimilar is a biological medicine that is highly similar to another already approved biological medicine, also known as the reference medicine, and is authorized in accordance with the same standards of quality, efficacy and safety as all biological treatments [6]. Biologicals have high molecular weight and a very complex three-dimensional structure. For that reason, creating exact copies of these medicines is impossible. Since modifications of the structure may impact the efficacy and safety of the product, the requirements for licensing biosimilars are more rigid than those for licensing generic drugs [19]. As the patents for Remicade® and Enbrel® already expired, biosimilars of infliximab and etanercept are now available [18]. CT-P13 is an IgG1 chimeric human-murine monoclonal antibody biosimilar of reference infliximab. It is the first biosimilar agent of infliximab and was approved in 2013 for the same therapeutic indications as the reference medicine [7, 13]. The efficacy and safety of CT-P13 is supported by 2 randomized controlled trials: PLANETAS and PLANTETRA [16, 25]. The PLANETAS study compared the pharmacokinetics, safety and efficacy of innovator infliximab and the biosimilar in patients with ankylosing spondylitis and found that the pharmacokinetic profiles of the two products are equivalent

and that the two agents have comparable safety and efficacy profiles [16]. The PLANTETRA study was performed on patients with rheumatoid arthritis and showed similar results [25]. The data regarding the use of biosimilars in psoriasis is promising but limited to case presentations or case series [5, 23]. Further research, is therefore mandatory to support the long-term safety and efficacy of the product.

Ethical aspects regarding the use of biologicals for the treatment of psoriasis

The development of biological therapies has revolutionized the management of psoriasis. Some ethical issues are however encountered when prescribing those therapies, the main concerns being drug safety, efficacy, accessibility and cost [21]. While those drugs proved very efficient, they act by decreasing the immune system response and are associated with serious adverse reactions. Therefore, the dermatologist must carefully select those patients who are adequate candidates for biological treatment and explain to them the risks and benefits associated with those therapies.

There are some ethical concerns regarding the interchangeability and substitution of biosimilars. With generic drugs, changing one drug with another one with the same International Non-proprietary Name (INN) is considered acceptable. Biosimilars however are large molecules with a complex structure. Switching a patient which is responding well to the innovator drug, to a biosimilar in order to reduce costs without the intervention of the prescribing physician and the consent of the patient raises some ethical issues. The legislation regarding biosimilar substitution is different in various European countries. Therefore, in some countries automatic substitution in the pharmacy is not allowed while in others automatic substitution must be actively prohibited by the physician [8, 17, 18].

The objective of the present study was to compare the efficacy of the infliximab biosimilar to the efficacy of methotrexate in patients with moderate to severe plaque type psoriasis; the first biosimilar available worldwide for the treatment of psoriasis *versus* the standard conventional systemic therapy.

Materials and Methods

The retrospective study was conducted in the Dermatology Department of “Dr. Victor Babeș” Hospital for Infectious and Tropical Diseases in Bucharest, Romania. It was performed on men and women older than 18 years of age who were diagnosed with moderate to severe psoriasis and were unresponsive to topical therapies and therefore candidates for systemic treatment. The diagnosis of psoriasis was confirmed in all patients by histopathological examination. Patients treated

with infliximab biosimilar were also candidates for biological treatment [14]. Naïve patients and patients who had previously received biological treatments were included. Each enrolled patient signed a written informed consent. The infliximab biosimilar, provided to the patients through the National Program for the treatment of patients with moderate and severe psoriasis, was administered as an intravenous infusion of 5 mg/kg at weeks 0, 2 and 6 followed by a maintenance regimen of 5 mg/kg every 8 weeks. Oral methotrexate was administered as 15 mg/week divided in three equal doses over 24 hours. The severity of the disease was measured using the Psoriasis Area and Severity Index (PASI) at the beginning of the treatment (day 0) and then at 3, 6, 9 and 12 months. PASI is a clinical scale used to measure the severity of psoriasis based on the area coverage and plaque characteristics (intensity of erythema, thickness and scaling). It ranges from 0 (no disease) to 72 (the most severe case). The primary efficacy endpoint was the proportion of patients achieving an improvement of at least 75% in the PASI (PASI 75) at months 3, 6, 9, 12. The secondary efficacy endpoint was the proportion of patients achieving an improvement of at least 90% in the PASI (PASI 90) at months 3, 6, 9, 12. Demographic data, previous treatments and adverse events were also noted.

Statistical analysis

Continuous variables are presented as mean ($\pm$ standard deviation); mean comparisons employed Student t-test or Mann-Whitney U test, as appropriate after data normality assessment. Changes of PASI over time were evaluated by mixed-design repeated

measures analysis of variance (split-plot ANOVA) using Bonferroni adjustment for multiple comparisons, assessing for time*treatment interaction, as well as simple main effects. Time-to-event analysis was performed using Kaplan-Meier survival curves; the Mantel-Cox log-rank test was used to examine the equality of PASI improvement cumulative distributions across the two treatment groups. Hazard ratios were assessed by Cox proportional regression model adjusted for treatment groups. We chose a significance level of 0.05 and a confidence interval of 95% for hypothesis testing. Statistical analyses were performed using SPSS statistics Version 20 (IBM Corp., NY, USA).

Results and Discussion

16 patients treated with infliximab biosimilar and 30 patients treated with methotrexate were included in the study. The mean age of patients who received infliximab biosimilar was 55.69 (12.25) years and the mean age of patients who received methotrexate was 48.17 (15.68) years. The age difference was not statistically significant ($p > 0.05$). The mean age at onset was 39.25 (18.41) for patients treated with infliximab biosimilar and 32.47 (12.74) for patients treated with methotrexate. The difference was not statistically significant ($p > 0.05$). The male to female ratio was similar for the two groups (11:5 for infliximab biosimilar, 19:11 for methotrexate) (Table I). Five patients from the infliximab biosimilar group had been previously treated with biological therapies (3 with etanercept and 2 with adalimumab).

Table I

Demographic data and disease characteristics for the studied patients. Data are presented as mean and standard deviation (SD)

	Treatment				p value
	Methotrexate (n = 30)		Infliximab biosimilar (n = 16)		
	Mean	SD	Mean	SD	
Age (years)	48.1	15.68	55.6	12.25	0.103
Sex (male/female ratio)	1.72		2.2		0.72
Onset age of disease	32.4	12.74	39.2	18.41	0.149
Demographics (urban/rural ratio)	1.72		1.66		0.957
PASI Baseline	20.38	5.26	22.9	4.93	0.120
PASI 3 months	6.41	3.64	6.98	4.04	0.626
PASI 6 months	4.99	3.04	3.86	1.79	0.180
PASI 9 months	4.94	3.90	1.69	1.27	0.002
PASI 12 months	5.55	4.72	0.97	0.90	< 0.0

We have found a significant time X treatment interaction ($p < 0.01$) (Figure 1). The difference between the two treatments, measured by PASI, increases with time. In both treatment groups, there was a significant difference in PASI score from baseline to 3 months, as well as from 3 months to 6 months ($p < 0.05$). Between-subject analysis revealed

that mean PASI was similar for patients treated with methotrexate and patients treated with infliximab biosimilar (6.41 ± 3.64 versus 6.98 ± 4.04 , $p = 0.626$) at 3 months; superior results were obtained in the group treated with infliximab biosimilar. Statistically significant differences were obtained after nine months, favouring the improvement in disease

severity score in patients treated with infliximab biosimilar, as compared with patients treated with methotrexate (PASI 1.69 ± 1.27 versus 4.94 ± 3.9 , $p = 0.002$ at 9 months, 0.97 ± 0.9 versus 5.55 ± 4.72 , $p < 0.01$ at 12 months).

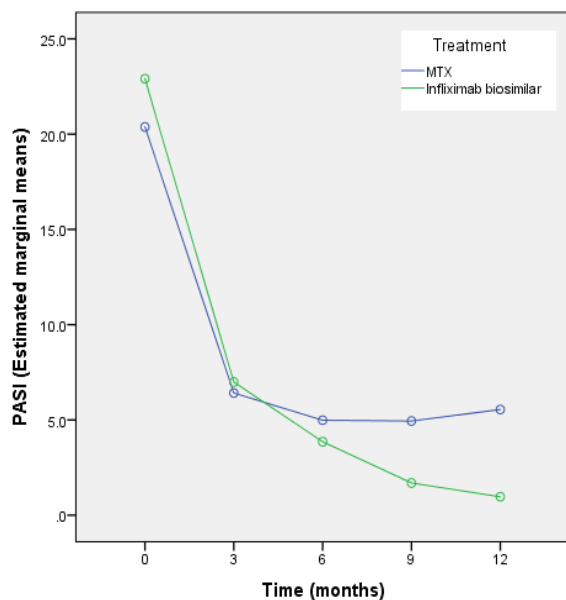


Figure 1.

PASI progression in time

After 3 months of treatment, a 75% improvement of the disease (PASI 75) was obtained in ten patients (62.5%) treated with infliximab biosimilar and nine patients (30%) treated with methotrexate. After 6 months, fifteen (93.75%) patients treated with infliximab biosimilar and seventeen (56.66%) patients treated with methotrexate achieved PASI75. All patients treated with infliximab biosimilar achieved PASI 75 in the first 9 months of treatment and the result was maintained until the next assessment, after the first 12 months of treatment. Twenty-two (73.3%) patients treated with methotrexate achieved PASI 75 after 9 months and this result was maintained by 12 months (Figure 2).

There was a significant difference between the two treatments ($p < 0.001$), as assessed by Mantel-Cox Log-rank test. Using Cox proportional regression model adjusted for treatment, we found that patients treated with infliximab biosimilar were 2.16 times (CI95%: 1.11 - 4.25, $p = 0.024$) more likely to achieve at least 75% improvement in PASI score (PASI75) than patients treated with methotrexate, during one year of treatment.

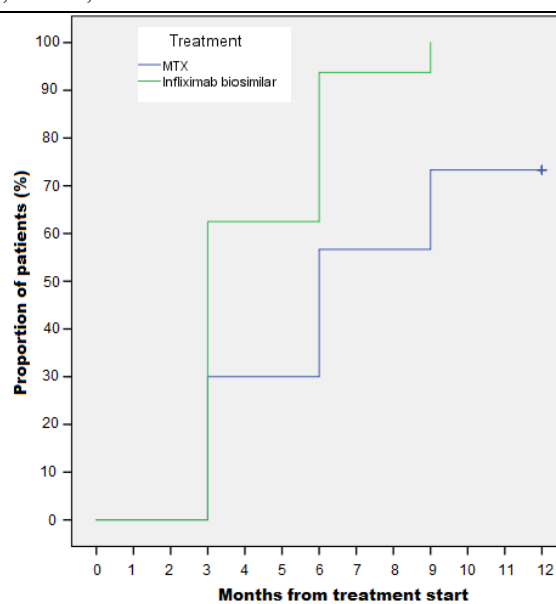


Figure 2.

Progression to PASI75

After 3 months of treatment two (12.5%) patients in the biosimilar infliximab group and two (6.66%) patients in the methotrexate group achieved PASI 90, while after 6 months three (18.75%) patients in the infliximab biosimilar group and four (13.33%) of those in the methotrexate group achieved PASI 90. After 9 months of treatment, a 90% improvement in the disease severity was obtained in fourteen (87.5%) patients treated with infliximab biosimilar and seven (23.33%) patients treated with methotrexate. The maximum results were obtained after 12 months of treatment when fifteen (93.75%) patients receiving infliximab biosimilar and twelve (40%) patients receiving methotrexate achieved PASI 90 (Figure 3).

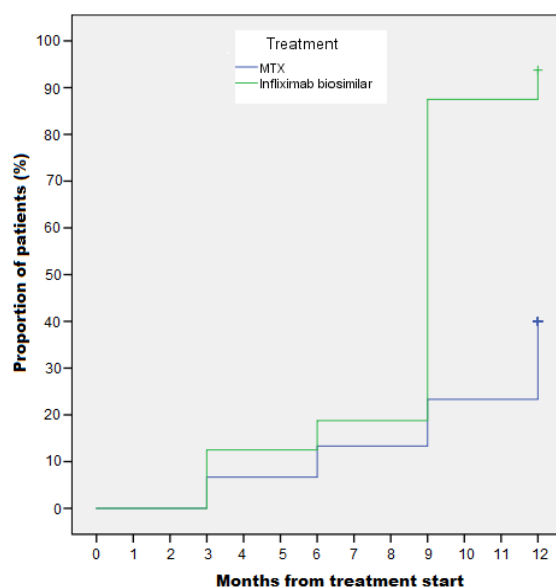


Figure 3.

Progression to PASI 90

In respect to the proportion of patients achieving PASI 90, the two treatments differed significantly, as assessed by Mantel-Cox Log-rank test ($p < 0.001$). Using Cox proportional regression model adjusted for treatment, we found that patients treated with infliximab biosimilar were 3.56 times (CI95%: 1.61 - 7.83, $p = 0.0017$) more likely to achieve at least 90% improvement in PASI score (PASI 90) than patients treated with methotrexate, during one year of treatment.

The safety of the two treatments was also evaluated. Two patients treated with infliximab biosimilar (2/16) and 10 patients treated with methotrexate (10/30) had elevated levels of transaminases (2 - 3 x upper limit of normal). Infusion reactions were seen in 3 (3/16) patients treated with infliximab biosimilar. Nausea was reported by 3 patients (3/30) and headaches were reported by 2 patients (2/30) treated with methotrexate. All the adverse events encountered were mild and did not require treatment cessation.

In this study we found that the efficacy of infliximab biosimilar, as measured by PASI 75 and PASI 90, was significantly higher than the efficacy of methotrexate. Significantly more patients treated with the biosimilar of infliximab achieved a 75% improvement than patients treated with methotrexate and the superior results were noticed from the first 3 months of treatment. Most patients achieved PASI 90 after 9 months of treatment.

Dapavo *et al.* studied the efficacy of biosimilar infliximab in patients with psoriasis. The authors found that four out five patients achieved PASI 75 after 10 weeks of treatment. The authors also found that patients who changed the reference product to the biosimilar maintained their clinical response [5]. Very few studies compared the efficacy and safety of biological therapies with that of methotrexate. RESTORE1 was an open-label randomized trial which compared the safety and efficacy of infliximab to that of methotrexate in patients with psoriasis. 868 patients were randomized 3:1 to receive infliximab or methotrexate. At week 16, PASI 75 was achieved in 78% of patients treated with infliximab and 42% of those treated with methotrexate [2].

CHAMPION was a randomized, double blind, double-dummy placebo-controlled study which evaluated the efficacy and safety of adalimumab *versus* methotrexate *versus* placebo in psoriatic patients. 271 patients were randomized in a 2:2:1 ratio to receive adalimumab, methotrexate or placebo. At week 16, 79.6% of patients treated with adalimumab, 35.5% of those treated with methotrexate and 18.8% of those receiving placebo achieved PASI 75 [22]. Moreover, Reich *et al* compared the risk-benefit profile of adalimumab, methotrexate and placebo using data from CHAMPION and found that adalimumab is associated with substantially more days free of any adverse events, moderate to

severe adverse events, infection-related adverse events and drug-related adverse events and concluded that adalimumab has a superior benefit-risk profile to methotrexate and placebo [20].

A randomized, double-blind, phase 3 trial published in 2017 compared the efficacy and safety of adalimumab 0.8 mg/kg, adalimumab 0.4 mg/kg and methotrexate in children and adolescents with severe chronic plaque psoriasis. At week 16, 58% of patients receiving adalimumab 0.8 mg/kg, 44% of patients receiving adalimumab 0.4 mg/kg and 32% of patients receiving methotrexate achieved PASI 75. The authors therefore concluded that adalimumab 0.8 mg/kg is associated with significant improvements in PASI 75 in children and adolescents [15].

The introduction of biosimilars is expected to lead to important cost related savings which could be used to treat additional patients [9]. It is also expected that biosimilars will bring down the price of the reference products thus leading to additional savings [17].

To the best of our knowledge, this is the first study comparing the efficacy of infliximab biosimilar to that of methotrexate. The limitations of the study are the small number of patients and the relative short length of follow-up, for 12 months. Further multicentre studies enrolling a larger number of patients followed for a longer period of time would clarify the extent of differences in regard to the efficacy of the two treatments.

Conclusions

In this study we found that the infliximab biosimilar proved significantly higher efficacy and more rapid clinical improvement than methotrexate in patients with moderate to severe psoriasis. Patients receiving infliximab biosimilar were over 2 times more likely to achieve an improvement of 75% in disease severity and over 3 times more likely to achieve an improvement of 90% during one year of treatment than patients receiving methotrexate. Our study therefore suggests that infliximab biosimilars are efficient therapies in moderate and advanced stages of plaque-type psoriasis.

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References

1. Al Sawah S., Foster S.A., Goldblum O.M., Malatestinic W.N., Zhu B., Shi N., Feldman S.R.,

- Healthcare costs in psoriasis and psoriasis subgroups over time following psoriasis diagnosis. *J. Med. Econ.*, 2017; 20(9): 982-990.
2. Barker J., Hoffmann M., Wozel G., Ortonne J.P., Zheng H., Van Hoogstraten H., Reich K., Efficacy and safety of infliximab vs. methotrexate in patients with moderate to severe plaque psoriasis: results of an open label, active controlled, randomized trial (RESTORE1). *Br. J. Dermatol.*, 2011; 165(5): 1109-1117.
3. Bărcă M., Manda G., Ciobanu A.M., Bălălaşu C., Lupuleasa D., Burcea Dragomiroiu G.T.A., Pop A., Popa D.E., Baconi D.L., Immunomodulatory effects of methadone following methotrexate therapy in a rat model of arthritis. *Farmacia*, 2017; 53(3): 423-428.
4. Braun-Falco O., Plewig G., Wolff H., Landthaler M., Braun-Falco's Dermatology. 3rd edition. Springer, 2009; 506-518.
5. Dapavo P., Vujic I., Fierro M.T., Quaglini P., Sanlorenzo M., The infliximab biosimilar in the treatment of moderate to severe plaque psoriasis. *J. Am. Acad. Dermatol.*, 2016; 75(4): 736-739.
6. European Medicines Agency. Biosimilar Medicines. <http://www.ema.europa.eu>.
7. Gabbani T., Deiana S., Annese V., CT-P13: design, development, and place in therapy. *Drug Des. Devel. Ther.*, 2017; 11: 1653-1661.
8. GaBI online – biosimilar substitution in the EU. <http://gabionline.net>.
9. Jha A., Upton A., Dunlop W.C., Akehurst R., The budget impact of biosimilar infliximab (Remsima[®]) for the treatment of autoimmune diseases in five European countries. *Adv. Ther.*, 2015; 32(8): 742-756.
10. Kimball A.B., Jacobson C., Weiss S., Vreeland M.G., Wu Y., The psychosocial burden of psoriasis. *Am. J. Clin. Dermatol.*, 2005; 6(6): 383-392.
11. Łakuta P., Marcinkiewicz K., Bergler-Czop B., Brzezińska-Weisło L., How does stigma affect people with psoriasis?. *Postepy. Dermatol. Alergol.*, 2017; 34(1): 36-41.
12. Mazur M., Olek-Hrab K., Karczewski J., Teresiak-Mikołajczak E., Adamski Z., Biosimilars in dermatology. *Postepy. Dermatol. Alergol.*, 2015; 32(5): 384-387.
13. McKeage K., A review of CT-P13: an infliximab biosimilar. *BioDrugs*, 2014; 28(3): 313-321.
14. Ministry of Health. National Programme for the treatment of medium and high severity *psoriasis vulgaris* patients. <http://www.ms.ro>.
15. Papp K., Thaçi D., Marcoux D., Weibel L., Philipp S., Ghislain P.D., Landells I., Hoeger P., Kotkin C., Unnebrink K., Seyger M., Efficacy and safety of adalimumab every other week versus methotrexate once weekly in children and adolescents with severe chronic plaque psoriasis: a randomised, double-blind, phase 3 trial. *Lancet*, 2017; 390(10089): 40-49.
16. Park W., Hrycaj P., Jeka S., Kovalenko V., Lysenko G., Miranda P., Lee S.J., A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann. Rheum. Dis.*, 2013; 72(10): 1605-1612.
17. Puig L., Biosimilars and reference biologics: decisions on biosimilar interchangeability require the involvement of dermatologists. *Actas Dermosifiliogr.*, 2014; 105(5): 435-437.
18. Puig L., Biosimilars in psoriasis 2015: what is next?. *J. Eur. Acad. Dermatol. Venereol.*, 2016; 30(3): 467-469.
19. Ranjan N., Mahajan V.K., Misra M., Biosimilars: The 'future' of biologic therapy?. *J. Dermatolog. Treat.*, 2011; 22(6): 319-322.
20. Reich K., Signorovitch J., Ramakrishnan K., Andrew P.Y., Wu E.Q., Gupta S.R., Bao Y., Mulani P.M., Benefit-risk analysis of adalimumab versus methotrexate and placebo in the treatment of moderate to severe psoriasis: Comparison of adverse event-free response days in the CHAMPION trial. *J. Am. Acad. Dermatol.*, 2010; 63(6): 1011-1018.
21. Santoro F.A., Rothe M.J., Strober B.E., Ethical considerations when prescribing biologics in dermatology. *Clin. Dermatol.*, 2012; 30(5): 492-495.
22. Saurat J.H., Stingl G., Dubertret L., Papp K., Langley R.G., Ortonne J.P., Unnebrink K., Kaul M., Camez A., Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br. J. Dermatol.*, 2008; 158(3): 558-566.
23. Tichy M., Kopova R., Sternbersky J., First experience with therapy of severe forms of psoriasis with biosimilar infliximab. *J. Eur. Acad. Dermatol. Venereol.*, 2016; 30(3): 491-493.
24. Wolff K., Goldsmith L., Katz S., Gilchrest B., Paller A., Leffell D., Fitzpatrick's Dermatology in General Medicine. Mc. Graw-Hill Professional; Seventh edition. 2007; 169-193.
25. Yoo D.H., Hrycaj P., Miranda P., Ramiterre E., Piotrowski M., Shevchuk S., Kovalenko V., Prodanovic N., Abello-Banfi M., Gutierrez-Ureña S., Morales-Olazabal L., Tee M., Jimenez R., Zamani O., Lee S.J., Kim H., Park W., Müller-Ladner U., A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann. Rheum. Dis.*, 2013; 72(10): 1613-1620.