

Ten-year Followup of Infliximab Therapy in Rheumatoid Arthritis Patients with Severe, Longstanding Refractory Disease: A Cohort Study

Filip De Keyser, Joris De Kock, Hermine Leroi, Patrick Durez, René Westhovens, and the Infliximab EAP Study Group

ABSTRACT. Objective. Our study describes the 10-year followup data of the Belgian Expanded Access Program (EAP) for infliximab (IFX), which included patients with active rheumatoid arthritis who were refractory to methotrexate. The objectives of the study were to evaluate the continuation rate, reasons for discontinuation, and longterm disease control under IFX treatment, and to study baseline characteristics associated with longterm successful IFX therapy.

Methods. Between February 2000 and September 2001, 511 patients were enrolled in the Belgian IFX EAP, and 507 effectively started IFX therapy. Previously reported data showed that 160 patients were still treated with IFX after 7 years of followup. We describe the therapy status, reasons for IFX discontinuation, and the level of disease activity of this subgroup after 10 years of followup. Baseline characteristics of the total EAP cohort were used to describe variables associated with longterm successful IFX treatment.

Results. After 10 years of followup, 110 of the 507 patients (21.7%) were still receiving IFX treatment. In the 7-year to 10-year period, which is the focus of the current study, 16 patients were lost to followup and 34 patients discontinued IFX treatment, mainly because of loss of efficacy. Patients successfully treated with IFX for 10 years had lower baseline values for 28-joint Disease Activity Score (DAS28), patient pain scale, physician visual analog scale, and Health Assessment Questionnaire in comparison with the rest of the study cohort. The mean DAS28 level of the subgroup still taking IFX after 10 years was 2.55 ± 1.01 .

Conclusion. In the Belgian EAP, 21.7% of patients continued to receive maintenance IFX treatment after 10 years of followup. IFX provided good longterm disease control in these patients. (First Release June 1 2014; J Rheumatol 2014;41:1276–81; doi:10.3899/jrheum.131270)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
COHORT STUDY

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INFLIXIMAB
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Because the inflammatory cytokine tumor necrosis factor (TNF) plays a key role in the pathophysiology of rheumatoid arthritis (RA), TNF inhibitors were the first class of biologicals on the market for the treatment of RA. They have

become standard treatment for patients with active disease refractory to treatment with classic disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX).

A large number of randomized controlled trials has demonstrated the short-term effectiveness and safety of these agents¹, but data on the longterm efficacy and safety largely depend on registries and cohort studies².

Infliximab (IFX), a chimeric monoclonal antibody against TNF, in combination with MTX, has been shown to be both effective and safe for treating RA³. The Belgian Expanded Access Program (EAP) for IFX enrolled patients with RA starting to take IFX treatment between February 2000 and September 2001. Previous publications described results from the EAP cohort after 1, 4, and 7 years of followup^{4,5,6}. We describe 10-year followup data of the cohort. The aims of our study were to evaluate the IFX continuation rate, longterm disease activity control, and reasons for discontinuation of IFX treatment. Also, the baseline characteristics of the subgroup of patients who successfully continued IFX over the 10-year period were compared with the rest of the EAP cohort.

From Department of Rheumatology, Ghent University, Ghent; MSD Belgium BVBA; Department of Rheumatology, Pôle de Recherche en Rhumatologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels; Skeletal Biology and Engineering Research Center, Department of Development and Regeneration KU Leuven; and Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium.

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F. De Keyser, MD; J. De Kock, MD, Department of Rheumatology, Ghent University; H. Leroi, MSD Belgium BVBA, Brussels; P. Durez, MD, Department of Rheumatology, Pôle de Recherche en Rhumatologie, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain and Cliniques Universitaires Saint-Luc; R. Westhovens, MD, PhD, Skeletal Biology and Engineering Research Center, Department of Development and Regeneration KU Leuven; and Department of Rheumatology, University Hospitals Leuven.

Address correspondence to Prof. De Keyser, Ghent University Hospital OK12, Department of Rheumatology, De Pintelaan 185, B-9000 Ghent, Belgium. E-mail: filip.dekeyser@ugent.be

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Our study represents a substantial cohort of patients treated for a full decade with IFX, and to our knowledge, one of the longest periods of systematic followup in patients with RA under IFX treatment.

MATERIALS AND METHODS

Study design and population. Between February 2000 and September 2001, 511 patients were enrolled in the Belgian EAP cohort for IFX in RA; 507 patients effectively started IFX treatment. These patients were the first Belgian patients with RA to be treated with IFX outside the setting of a clinical trial. Before June 2002, the start of IFX reimbursement in Belgium, the drug was provided free of charge by Schering-Plough (now MSD) as part of a Medical Need Program.

Patients qualified for inclusion in the program if they were between 18 and 80 years old, fulfilled the American College of Rheumatology criteria for RA and had active disease refractory to at least 2 DMARD, including MTX. Exclusion criteria were limited to contraindications for IFX treatment.

Patients from different academic and nonacademic centers participated in the study. The study was approved by the ethics committees of all participating centers, and all patients gave their written informed consent before inclusion in the study.

IFX was administered as intravenous infusions at a standard dose of 3 mg/kg on weeks 0, 2, and 6, and every 8 weeks thereafter. In case of insufficient disease control or flare, patients could receive an additional 100 mg dose⁴.

Data collection. A flowchart of the study is presented in Figure 1. Patients who were still under IFX treatment at the 7-year followup timepoint were contacted for the 10-year followup evaluation.

Data collected from all patients at the 10-year followup evaluation included the date of first IFX infusion, current treatment status, IFX dosing regimen, and additional treatments. Clinical evaluation included the Health Assessment Questionnaire (HAQ) and 28-joint Disease Activity Score-erythrocyte sedimentation rate (DAS28-ESR)⁷.

For patients who had stopped IFX treatment, we recorded the reason for discontinuation, the date of last IFX infusion, and the followup biologic drug, in the event of a switch to an alternative.

Data analysis and statistics. Data are presented as mean \pm standard error of the mean (SE), or as percentages. Statistical analysis was performed with SPSS 20 (IBM Corporation). Normal distribution of variables was assessed with the Kolmogorov-Smirnov test. For comparisons between the 10-year cohort and the overall study population, t-test was used for normally distributed variables and the Mann-Whitney U test for variables that were not normally distributed.

RESULTS

Course of the study. The course of the study is summarized in the flowchart of Figure 1.

At the 7-year followup timepoint, the cohort consisted of 441 evaluable patients, with 160 patients still receiving treatment⁶. Ten years after the start of the study, 144 of the 160 patients who continued IFX therapy after 7 years were evaluated for treatment status and disease activity. After 10 years of followup, 110 of the 144 evaluable patients continued therapy (76.4% of evaluable patients, 21.7% of the intention-to-treat population).

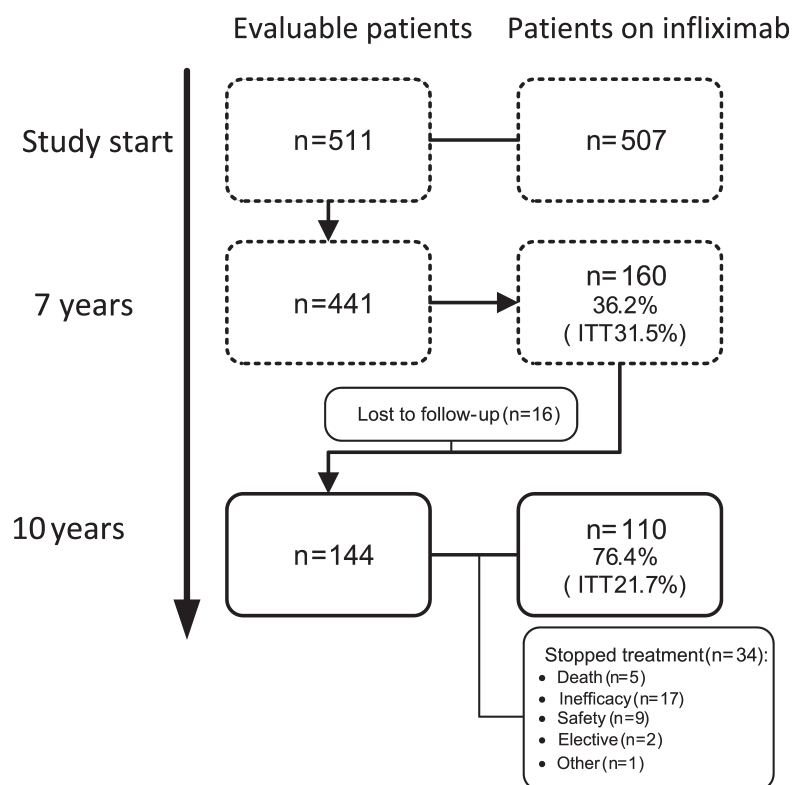


Figure 1. Flow chart of the Expanded Access Program for infliximab (IFX) in the Belgian cohort. The 160 patients still receiving IFX treatment after 7 years of followup were invited for the 10-year evaluation. Of 144 evaluable patients, 110 were still receiving IFX treatment after 10 years of followup. ITT: intention-to-treat.

Population characteristics. Table 1 provides an overview of the baseline characteristics of 2 complementary study population subgroups, comparing the patients who successfully continued IFX treatment for 10 years to the remainder of the cohort. In comparison with the rest of the study population, several baseline disease activity variables were lower in patients who remained on IFX for the full 10-year followup period: DAS28, the number of tender joints, HAQ score, patient pain scale score, and patient and physician global VAS at baseline were significantly lower in the patients who remained on IFX successfully for at least 10 years in comparison to the rest of the cohort.

Followup, treatment retention, and reasons for discontinuation. After 10 years of followup, 110 of the 507 patients (21.7%) were still receiving IFX treatment. In the 7–10 year period, 16/160 patients (10%) were lost to followup, 34 of 144 evaluable patients (23.6%) stopped IFX treatment, half of them (17/34) because of loss of efficacy. Reasons for IFX discontinuation in this period are detailed in Figure 2. In the safety category, infection was the main reason for discontinuing IFX (4/9 patients). The infections leading to IFX discontinuation were interbuttock abscess, sepsis with *Streptococcus pyogenes* combined with septic arthritis of the knee, cutaneous infection, and 3 episodes of bronchitis requiring hospitalization within 1 year. Malignancy was the reason for discontinuation in only 1 patient. Five people died in this period, 2 of them of lung cancer.

In the patient group remaining on IFX treatment after 10 years of followup, 78/110 patients received the standard IFX dosing regimen of 3 mg/kg every 8 weeks; 15/110 patients received an extra 100 mg vial of IFX every 8 weeks,

whereas 17/110 patients intermittently received an extra vial when needed.

IFX was used in combination with MTX in 98/110 (89.1%) patients treated over the 10-year period, at a mean dose of 9.6 ± 0.8 mg/week, while 30/34 (88.2%) of patients who discontinued IFX treatment in the 7–10 year followup timepoint were taking MTX, at a mean dose of 9.7 ± 1.4 mg/week. Of the patients continuing IFX treatment, 41/110 (37.2%) were concurrently treated with corticosteroids, whereas 22/34 (64.7%) of patients who stopped IFX treatment used corticosteroids ($p < 0.05$).

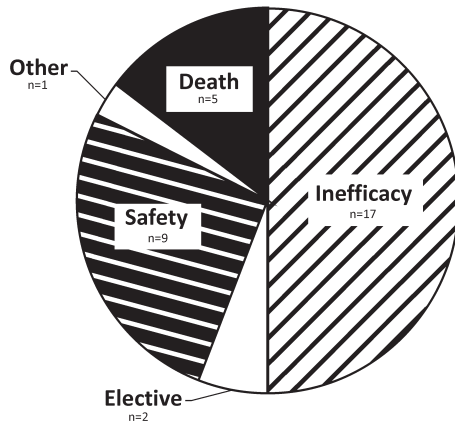
After stopping IFX treatment, 21/34 patients were switched to another biologic: 4 patients received rituximab, 8 patients received etanercept, 3 received adalimumab, and 2 patients each were switched to abatacept and tocilizumab, respectively; and for 2 patients the name of the alternative biological was not known. One patient was switched from etanercept to certolizumab pegol within the followup period of the study.

Longterm disease control with IFX. Figure 3 shows the evolution of DAS28 over time in the cohort of 144 patients still receiving IFX at 7 years and followed under this study until 10 years, with respect to their treatment status at 10 years or the reason for IFX discontinuation. Patients continuing IFX treatment for 10 years had DAS28 values of 2.63 ± 0.96 and 2.55 ± 1.01 after 7 and 10 years of treatment, respectively, while patients who stopped treatment had DAS28 values of 4.03 ± 1.06 and 2.78 ± 0.95 at these timepoints. The difference of 10-year HAQ scores versus baseline HAQ in patients taking treatment (0.35 ± 0.71) and in patients who stopped between years

Table 1. Baseline characteristics of 2 complementary Expanded Access Program (EAP) study population subgroups. Baseline characteristics of patients who successfully continued infliximab (IFX) treatment for 10 years are compared with those of the remainder of the cohort. Data are \pm SD unless otherwise indicated.

Characteristics	Patients Taking Infliximab After 10 yrs, n = 110	Rest of the EAP Cohort, n = 397	p
Age, yrs	46.1 \pm 2.2	46.5 \pm 1.5	0.885
Sex, % female	72.4	71.7	0.879
Disease duration, yrs	11.5 \pm 0.7	11.2 \pm 0.6	0.833
RF positivity, %	72.7	79.4	0.241
DAS28	5.69 \pm 0.11	5.97 \pm 0.07	0.025*
ESR, mm/h	31.4 \pm 2.1	34.4 \pm 1.4	0.243
CRP, mg/l	25.9 \pm 2.3	30.6 \pm 2.0	0.182
Tender joints	18.30 \pm 1.02	21.30 \pm 0.65	0.014*
Swollen joints	14.89 \pm 1.02	15.33 \pm 0.46	0.596
HAQ	1.53 \pm 0.05	1.66 \pm 0.03	0.03*
Patient pain scale, mm	57.1 \pm 1.8	63.8 \pm 1.1	0.02*
Patient global VAS, mm	60.4 \pm 1.8	65.7 \pm 1.1	0.011*
Patient fatigue, mm	63.7 \pm 2.0	66.7 \pm 1.2	0.193
Physician global VAS, mm	53.5 \pm 1.6	62.4 \pm 1.0	< 0.001*

For normally distributed variables t-test was applied, and for non-normally distributed variables Mann-Whitney U test; chi-square test was used for categorical variables. *Statistically significant values. CRP: C-reactive protein, DAS28: disease activity score using 28 joint counts, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire; VAS: visual analog scale; RF: rheumatoid factor.



Death	n
Lung carcinoma	2
Cardiovascular collapse	1
unknown	2

Safety	n
Infection	4
Breast cancer	1
Infusion reaction	1
Arthralgia	1
Neuropathy	1
Psoriasis	1

Elective	n
Planned surgery	1
Pregnancy wish	1

Other	n
IV access problem	1

Figure 2. Reasons for infliximab discontinuation in the 7 to 10-year period. IV: intravenous.

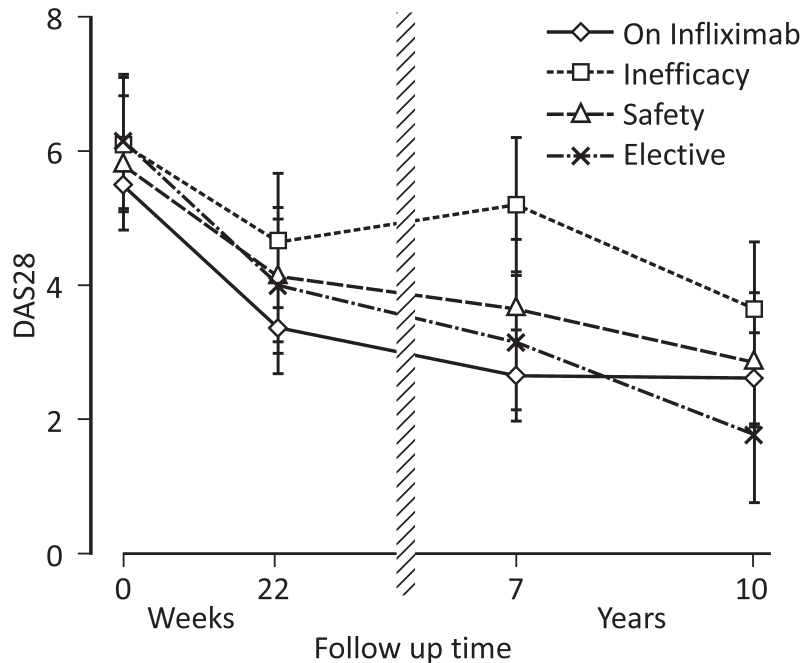


Figure 3. Evolution of disease activity over time. Disease activity score in 28 joints (DAS28) over time in the patients still under infliximab (IFX) at year 7 and followed for 10 years after starting IFX treatment. Patients were categorized according to treatment status, distinguishing patients remaining on IFX treatment for 10 years (n = 110) from patients who stopped treatment during the 7 to 10-year followup period, presented according to the reason for discontinuation (inefficacy: n = 17, safety: n = 9, elective: n = 2).

7 and 10 (0.11 ± 0.57) did not differ significantly (ANOVA, $p = 0.18$).

DISCUSSION

In our study we describe 10-year followup data of patients

with RA who started IFX treatment in the context of the Belgian EAP for this drug. The EAP study prospectively collected treatment continuation and efficacy data of IFX treatment in a large cohort of patients with RA, spanning a full decade, with very limited loss of patients to followup.

The chronic character of RA, requiring patients to receive drug treatment for many years, dictates the need for longterm data on the efficacy and safety of drugs used to treat this disease. Longterm treatment data in general come from extensions of controlled trials or from registry studies. The current study occupies a fairly unique position, in that it combines an unbiased consecutive patient inclusion with inclusion criteria similar to the daily clinical practice reimbursement criteria, with a limited time span of inclusion and a systematic followup, allowing analysis of trends over time as in an inception cohort.

Interestingly, patients successfully treated with IFX for a period of at least 10 years had lower baseline values for a number of disease activity variables (DAS28, number of tender joints, patient pain scale, patient and physician VAS and HAQ) in comparison with the rest of the study population.

In the EAP cohort, drug retention rates were relatively high, with 61.6%, 36.2%, and 21.7% of patients still receiving IFX treatment after four⁵, seven⁶, and 10 years (current study) of followup, respectively. Reported figures on biologic retention rates in RA are difficult to interpret, because the sources on which these reports are based, the duration of followup, and the patient characteristics described are quite heterogeneous. The daily practice setting and the possibility of some dosing flexibility as described in the results might be partly responsible for the high retention rates; on the other hand, the patients in the EAP were a selection of the most refractory patients at the time of program start. Patients who continued IFX for 10 years had a mean DAS28 of 2.55, which is very acceptable given the initial selection of patients. The subgroups of patients at 7 years with high DAS exactly reflects the patients in whom later on (between 7 and 10 yrs) IFX therapy was stopped because of inefficacy. One may wonder whether a certain reluctance to stop a drug that has provided acceptable disease control for years may explain why DAS28 values at 7 years were relatively high, at least in a subgroup of patients. However, as stated, it was this subgroup who was switched to another therapy regimen between 7 and 10 years of followup.

The anti-TNF therapy survival rate in a Swiss cohort study fell below 50% after 3 years, for all 3 anti-TNF drugs under study (IFX, etanercept, adalimumab)⁸. In the Danish national registry DANBIO, covering 2326 patients with a cumulative followup of 1161 patient-years, IFX treatment survival after 48 months was 56%⁹. The Italian GISEA registry reported IFX therapy retention of 37.6% after 4 years, which is much lower than in our study¹⁰. In a recent Greek study in which IFX-treated patients were followed for 7 years, treatment survival was observed to be high in the first years of treatment but decreased considerably after the fifth year of treatment¹¹. This observation contrasts with the findings in the current EAP cohort, because the percentage

decline in IFX therapy continuation remained more or less constant over the 10-year study period.

Loss of efficacy is often reported as the main reason for discontinuing anti-TNF treatment. In the EAP cohort, half the patients who stopped IFX treatment between the 7-year and 10-year followup timepoints did so because of loss of efficacy. Formation of anti-IFX antibodies may be one of the factors associated with loss of efficacy^{12,13}. The presence of anti-IFX antibodies was not evaluated in the present study. The individual character of the dose-response curve may also have an influence on IFX efficacy, because IFX trough levels were shown to predict sustained disease control under IFX treatment¹⁴. IFX treatment has been shown to decrease rheumatoid factor (RF) IgM titers, but these changes did not correlate well with the response to treatment¹⁵. In the EAP cohort, the percentage of RF-positive patients was not different in the subgroup treated successfully for 10 years, in comparison with the rest of the study population. It was technically not possible to quantitatively follow RF titers over the whole study period. Thus, the effect of longterm successful IFX therapy on this antibody titer could not be assessed.

A Japanese prospective study with 636 patient-years of followup in 412 IFX-treated patients reported that the risk of serious infections was mainly high during the first year of treatment¹⁶, while in a Belgian prospective study with 575 patients followed for 74 weeks after starting IFX treatment, adverse events and treatment discontinuations due to adverse events were mainly observed in the first half-year of treatment¹⁷. In the EAP population studied between 7 years and 10 years, only 4/34 patients discontinued treatment because of infection.

A metaanalysis found no elevated risk of malignancy with anti-TNF treatment¹⁸. Followup periods in most studies included in this metaanalysis were much shorter than the 10-year followup period we present here. The low number of malignancies observed in our study indicates that longterm treatment with IFX does not manifestly increase cancer risk. These findings are in line with a 2010 systematic review conducted by members of the European League Against Rheumatism Task Force¹⁹.

A study using data from the Swedish Biologics register found no difference in mortality rates between the anti-TNF drugs IFX, adalimumab, and etanercept²⁰. Another 2012 study found that mortality rates under anti-TNF treatment were comparable to mortality rates in the general population²¹.

Longterm treatment with IFX remains both safe and effective. In the Belgian IFX EAP cohort, more than one-fifth of patients remained under therapy after 10 years of followup. IFX provided good longterm disease control in these patients.

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APPENDIX

List of study collaborators. Members of the Infliximab EAP Study Group: Ackerman C, St-Lucas Ghent; Corluy L, Hasselt; Debrabanter G, St-Lucas Brugge; Declerck L, UZ Antwerpen; De Keyser F, Ghent University Hospital; Dhondt E, St-Jan Brugge; Durez P, Cliniques Universitaires Saint-Luc, Brussels; Herman L, Hamme; Hermans P, Ghent; Hoffman I, St-Augustinus Wilrijk; Janssens X, St-Lucas Ghent; Kruithof E, Elisabethziekenhuis Zottegem; Lensen F, H Serruysziekenhuis Oostende; Mielants H, Ghent University Hospital; Peretz A, CHU Brugmann, Brussels; Poriau S, AZ Alma Sijsele; Ravelingien I, OLV Aalst; Stuer A, Vandenbruwaene F, H-Hartkliniek Roeselaere; Vander Cruyssen B, Ghent University Hospital; Vanhooft J, Genk; Verbruggen L, AZ Vrije Universiteit Brussel; Volders P, Reumakliniek Genk; Westhovens R, University Hospitals K.U. Leuven.

REFERENCES

1. Aaltonen KJ, Virkki LM, Malmivaara A, Kontinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PLoS One* 2012;7:e30275.
2. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;CD008794.
3. Zintzaras E, Dahabreh IJ, Giannouli S, Voulgarelis M, Moutsopoulos HM. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. *Clin Ther* 2008;30:1939-55.
4. Durez P, Van den Bosch F, Corluy L, Veys EM, De Clerck L, Peretz A, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. *Rheumatology* 2005;44:465-8.
5. Vander Cruyssen B, Van Looy S, Wyns B, Westhovens R, Durez P, Van den Bosch F, et al. Four-year follow-up of infliximab therapy in rheumatoid arthritis patients with long-standing refractory disease: attrition and long-term evolution of disease activity. *Arthritis Res Ther* 2006;8:R112.
6. Vander Cruyssen B, Durez P, Westhovens R, De Keyser F. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. *Arthritis Res Ther* 2010;12:R77.
7. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
8. Du Pan SM, Dehler S, Ciurea A, Ziswiler H-R, Gabay C, Finckh A. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum* 2009;61:560-8.
9. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum* 2010;62:22-32.
10. Iannone F, Gremese E, Atzeni F, Biasi D, Botsios C, Cipriani P, et al. Longterm retention of tumor necrosis factor- α inhibitor therapy in a large Italian cohort of patients with rheumatoid arthritis from the GISEA registry: an appraisal of predictors. *J Rheumatol* 2012;39:1179-84.
11. Markatseli TE, Alamanos Y, Saougou I, Voulgari PV, Drosos AA. Survival of TNF-alpha antagonists in rheumatoid arthritis: a long-term study. *Clin Exp Rheumatol* 2012;30:31-8.
12. Pascual-Salcedo D, Plasencia C, Ramiro S, Nuño L, Bonilla G, Nagore D, et al. Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis. *Rheumatology* 2011;50:1445-52.
13. Yukawa N, Fujii T, Kondo-Ishikawa S, Yoshifuji H, Kawabata D, Nojima T, et al. Correlation of antinuclear antibody and anti-double-stranded DNA antibody with clinical response to infliximab in patients with rheumatoid arthritis: a retrospective clinical study. *Arthritis Res Ther* 2011;13:R213.
14. Mulleman D, Chu Miow Lin D, Ducourau E, Emond P, Ternant D, Magdelaine-Beuzelin C, et al. Trough infliximab concentrations predict efficacy and sustained control of disease activity in rheumatoid arthritis. *Ther Drug Monit* 2010;32:232-6.
15. Bruns A, Nicaise-Roland P, Hayem G, Palazzo E, Dieudé P, Grootenboer-Mignot S, et al. Prospective cohort study of effects of infliximab on rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies in patients with long-standing rheumatoid arthritis. *Joint Bone Spine* 2009;76:248-53.
16. Sakai R, Komano Y, Tanaka M, Nanki T, Koike R, Nagasawa H, et al. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1125-34.
17. Delabaye I, De Keyser F. 74-week follow-up of safety of infliximab in patients with refractory rheumatoid arthritis. *Arthritis Res Ther* 2010;12:R121.
18. Moulis G, Sommet A, Béné J, Montastruc F, Sailer L, Montastruc J-L, et al. Cancer risk of anti-TNF- α at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. *PLoS One* 2012;7:e48991.
19. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;69:976-86.
20. Simard JF, Neovius M, Askling J. Mortality rates in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: drug-specific comparisons in the Swedish Biologics Register. *Arthritis Rheum* 2012;64:3502-10.
21. Thyagarajan V, Norman H, Alexander K, Napalkov P, Enger C. Risk of mortality, fatal infection, and fatal malignancy related to use of anti-tumor necrosis factor- α biologics by rheumatoid arthritis patients. *Semin Arthritis Rheum* 2012;42:223-33.