Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: an achievable target?

Cost-effectiveness of biologic treatment for rheumatoid arthritis in clinical practice: An achievable target?

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Abstract

The burden of illness of rheumatoid arthritis (RA) falls on patients, families and society through the direct costs, indirect costs, and intangible costs. A large number of RA cost-of-illness studies have been performed in recent decades with discrepant results due to patient heterogeneity, and different health-care organization, employment rate or social support, job opportunities, and methodologies used to calculate the costs. The greatest burden of RA is the indirect and the intangible costs, but how to estimate them remains controversial. The systematic use of traditional disease modifying anti rheumatic drugs has changed the evolution of the disease. However, a considerable improvement in the management of RA has been obtained since the advent of biologic response modifiers. The use of these drugs, which have demonstrated greater efficacy than conventional therapies, have tripled the direct costs of RA, which rose from about € 4000 to roughly € 12,000, in a period of five years, from 2000 to 2005. The present paper is aimed to examine the effects of this change in therapeutic strategy.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory arthritis that affects approximately 1% of the population [1] and [2]. The course of RA varies but most patients present symmetric polyarthritis, clinically manifesting joint pain, stiffness and swelling. Untreated, most patients have a progressive course resulting in persistent pain, progressive joint destruction and short- and long-term disability. Disease activity is predominantly responsible for the disability in the early stages of RA, while non reversible joint damage increases disability later in the course of RA. In addition, patients with RA have increased mortality compared with the general population and this is frequently attributed to an increased risk of cardiovascular disease [3], [4] and [5].

The burden of illness of RA falls on patients, families and society through the direct costs (pharmacological, surgical and rehabilitative treatment, radiology, medical appointments, hospitalization, complementary and alternative medicine, transportation reimbursement, out-of-pocket expenses for caregivers), indirect costs (loss of work productivity) and intangible costs (cost of suffering with deterioration in the quality of life of patients, their families and friends) [6], [7], [8], [9], [10], [11] and [12]. The intangible costs are difficult to quantify and are not normally considered in studies on the cost of illness. A large number of RA cost-of-illness studies have been performed in recent decades with very different results. The discrepancies in the results probably come from the heterogeneity of the patient population (number of patients, differences in severity and duration of illness), different health-care organizations, different employment rate and social support, different job opportunities and different methodologies used to calculate the costs (friction cost method, human capital approaches, payers' perspective, social perspective) [11].

From the literature it is clear that the overall mean costs of RA amount to about €15,000 per year, while the direct annual costs of RA are on average about € 4000. However, the greatest burden of RA costs is the indirect costs, although consensus is lacking as to how to estimate them [10]. Different patient characteristics have an important influence on the costs of the illness. Indeed, the direct costs increase very significantly among the four functional classes of the American College of Rheumatology [6] and [8] and the cost increases in relation to the severity of the disease [13], [14] and [15]. There is also further evidence that higher scores on the health assessment questionnaire (HAQ)—the most commonly used tool for measuring the degree of disability—corresponds to increased worsening of the disease in the future, to greater morbidity and mortality, and to a progressive increase in the direct and indirect costs [11], [16], [17] and [18]. Comorbidity—above all cardiovascular disease, infections and depression has a heavy impact on disability [19], [20] and [21] resulting in an increase in costs, especially in patients with severe, long-standing disease [6], [11], [22] and [23].

Undoubtedly, the systematic use of traditional disease modifying anti rheumatic drugs (DMARDs) such as methotrexate, leflunomide and sulfasalazine has changed the evolution of the disease. Indeed, evidence indicates that the early use of DMARDs slows both joint erosion and progression of joint damage, and preserves function [24], [25], [26], [27], [28] and [29]. Non steroidal anti-inflammatory drugs (NSAIDS) and corticosteroids can reduce inflammation, control symptoms and lessen the functional limitations caused by disease activity. Moreover, there is evidence that if corticosteroids are used in association with DMARDS they can contribute towards slowing the progression of radiological lesions [30], [31], [32] and [33].

However, a considerable improvement in the management of RA has been obtained since the advent of biologic response modifiers. Nowadays, it is realistically possible to set clinical and radiological remission of the disease as the treatment objective and maintain these conditions over time. Indeed, these drugs can swiftly control the inflammatory processes and symptoms of the disease, thus improving the quality of life and inhibiting radiological alterations and anatomical damage, thereby enabling the patient to recover and maintain joint function [28], [34], [35] and [36]. The use of these drugs, which have demonstrated greater efficacy than conventional DMARDS in controlling the disease, have led to a 4-fold to 6-fold increase in the direct costs of RA [11] and [37], since it has been estimated that their annual cost ranges between US $16,000 and $20,000 compared to the approximately $3000 expense for the traditional DMARDs [38].

This has meant that in the last decade the cost of treating RA has progressively increased, above all due to the increased costs of treatment [39]. The findings of the PACTIS study in which patients took only traditional DMARDS [8] are paradigmatic compared to those of the Eco-PR study [13] where 20% of patients were treated with biologics. In a period of five years, from 2000 to 2005, the direct annual costs of RA tripled, rising from about €4000 to roughly €12,000.

This marked increase in costs has given rise to considerable anxiety in the national health agencies, and the cost-effectiveness of biologic drugs has become one of the highest priorities of health economics studies of RA. In the last decade numerous health economics surveys have been published on the use of anti TNF α biologic drugs in RA. Some years ago, an overview and a review of eight pharmacoeconomics studies on anti TNF α drugs [40] and [41] were presented, and very recently a systematic study was

published [39] on the cost-effectiveness of biologic drugs in RA in relation to traditional DMARDS, using two willingness-to-pay thresholds to assess cost-effectiveness: Can $50,000 and Can $100,000 per cost per quality-adjusted life year (QALY) gain. At a willingness-to-pay threshold of Can $50,000 per QALY gain the results can be summarised as follows: a) in patients with early RA who have never received methotrexate (MTX), starting with biologic drugs is not cost-effective compared to the use of MTX; b) in patients with RA

in whom MTX mono-therapy was not effective, the use of biologics in association with MTX was cost-effective compared to continuing with MTX alone; c) in patients in whom MTX combination therapy or sequential DMARDs administration was not effective, the use of biologics was not cost-effective. On the other hand, at a willingness-to-pay threshold of Can $100,000 per QALY gain, the results may be outlined thus: 1) the use of biologics in patients who have not previously undergone traditional DMARD treatment is only slightly cost-effective; 2) in patients in whom MTX in mono-therapy was not effective, the use of biologics was cost-effective; 3) in patients who had no response to treatment with MTX in combination with (an)other DMARD(s), introduction of the biologic drug into the treatment programme was cost-effective in 14 out of 35 comparisons. As regards other biologic drugs used in the treatment of rheumatoid arthritis, abatacept has been estimated to be cost-effective from the societal perspective in patients who do not respond to MTX and/or to the first TNFα inhibitor [42], [43], [44] and [45]. This is also true for rituximab when it is utilised in patients who fail to respond to the first TNFα, compared to another anti TNFα or a sequence of TNF inhibitors [43], [44], [45] and [46]. Rituximab seems to be the most cost-effective second line biologic drug [43], [44], [47] and [48]. A recent analysis has demonstrated that the use of tocilizumab is cost-effective if given after the failure of another biological DMARD or as an addition to the current standard of care in the treatment of RA with an inadequate response to DMARDs [49]. We have not found any pharmacoeconomic studies on golimumab or on certolizumab pegol. The drafting of the NICE guidelines [44] and EULAR criteria [42] and [50] for the management of RA also took into account the results of the pharmacoeconomics surveys on the cost-effectiveness of biologics.

Until the cost of biological drugs drops, the challenge is to optimise their use. This can be done through the early treatment of patients who do not respond to traditional DMARDs [39], as well as by identifying the group of patients in whom biologics can be successfully discontinued after a reasonable time without subsequent relapse of disease [11], or by identifying the subjects whose disease activity can be kept low by administering traditional DMARDs alone after the biologics. Indeed, the use of biologics after the MTX failure is cost-effective and there is evidence that these drugs can be successfully discontinued [51] and [52]. From an analysis of the BeSt study we evince that 51% of 115/508 patients achieved drug-free remission for a median duration of 23 months in the 5-year period [51]. In a study regarding a small number of cases, it was found that 42% of patients maintain low disease activity using A-Cyclosporin and MTX combination therapy: this low disease activity was obtained after 6–8 months with TNF α inhibitors and MTX [52]. Predictive factors of drug-free remission in patients with RA treated with biologics have yet to be precisely defined [53], although it can be hypothesised that such factors may be sought among the predictive factors for remission found in RA patients on anti-TNF drugs such as a lower baseline HAQ score, the concurrent use of NSAIDs, a higher number of previous DMARDs, RF negativity, age at baseline and male gender [54], [55] and [56].

Besides early treatment of RA to optimise the use of biologics, tight control of the disease is important [57], [58] and [59]. Indeed, this makes it possible to more easily achieve good clinical response,

remission, prevention of anatomical lesions and swifter recovery of the functional limitations in a short time. This can lead to a decrease in the use of health resources, and most markedly, in a reduction in expenses for surgical orthopaedic treatment, together with the possibility to discontinue the administration of biological drugs sooner. It would also be possible to have a reduction in the indirect costs involved in loss of work productivity.

It is interesting to highlight that the trend towards reducing the orthopaedic treatment of RA began before the use of biological drugs and coincided with the importance that the rheumatology community attributes

to early diagnosis and early use of DMARDs [11], [60] and [61]. In the context of countering disease activity early, and in order to achieve remission as soon as possible, thus saving health resources and permitting an earlier return to work, it is necessary to assess whether among the available biological drugs there are any faster acting drugs against the inflammatory process that can lead to swifter remission of disease activity. One such candidate might be tocilizumab in view of its rapidity in suppressing the inflammatory response [62] and in producing early inhibition of bone homeostasis [63]. Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumab pegol treatment was also shown to predict better long term outcomes in RA [64] and [65]. These elements might have a significant impact on earlier clinical improvement, prevention of joint damage and swifter recovery of function.

Considering the efficacy of synthetic DMARDs when they are used with a tight control strategy, together with recent evidence of how early response (within 1–3 months) to treatment with biological drugs is predictive of the response at 12 months, it would be interesting to know the effectiveness of tight control strategies utilising prompt cycling and swapping among various biological drugs.

As regards treatment side effects, it would also be useful to know whether there is any variability among the various biologics which might influence their cost-effectiveness. There might be a difference among TNF inhibitors: for instance, the data of the RATIO registry [66] and of the British Society for Rheumatology Biologics Register [67] reveal a similar incidence for opportunistic infections [66] and for severe infections [67], but a higher incidence of tubercular infections in patients treated with infliximab and adalimumab compared to etanercept. To answer these questions exhaustively, it would be important to conduct controlled head-head studies among the various biological drugs, also assessing possible associations with other drugs like DMARDs and steroids which could themselves increase the risks of infections. In particular, respiratory infections are among the most common causes of morbidity in the elderly and require considerable health resources, as well as also being a leading cause of death in RA. Respiratory infections have also been linked to the use of steroids and not only to TNF inhibitors and MTX [68] and [69]

In conclusion, in order to achieve the best cost-effectiveness in the treatment of RA in clinical practice, the factors that currently seem to play an important role are speed of action of the drug, tight control in patient management, and careful assessment of the safety profile of the various drugs.

References

[1] D.M. Lee, M.E. Weinblatt Rheumatoid arthritis Lancet, 358 (9285) (2001), pp. 903–911

[2] L. Moroni, I. Bianchi, Ana Lleo Geoepidemiology, gender and autoimmune disease. Autoimmun Rev (6–7) (May 11 2012), pp. A386–A392

[3] Z. Ozbalkan, C. Efe, M. Cesur, S. Ertek, N. Nasiroglu, K. Berneis et al. An update on the relationships between rheumatoid arthritis and atherosclerosis. Atherosclerosis, 212 (2) (Oct 2010), pp. 377–382

[4] N.J. Gullick, D.L. Scott. Co-morbidities in established rheumatoid arthritis. Best Pract Res Clin Rheumatol, 25 (4) (Aug 2011), pp. 469–483

[5] J.M. Anaya. Common mechanisms of autoimmune diseases. Autoimmun Rev, 11 (11) (Sep 2012), pp. 781–784 http://dx.doi.org/10.1016/j.autrev.2012.02.002 [Epub 2012 Feb 12]

[6] G. Leardini, F. Salaffi, R. Montanelli, S. Gerzeli, B. Canesi. A multicenter cost-of-illness study on rheumatoid arthritis in Italy. Clin Exp Rheumatol, 20 (4) (Jul-Aug 2002), pp. 505–515

[7] A.C. Rat, M.C. Boissier. Rheumatoid arthritis: direct and indirect costs. Joint Bone Spine, 71 (6) (Nov 2004), pp. 518–524

[8] F. Guillemin, S. Durieux, J.P. Daures, A. Lafuma, A. Saraux, J. Sibilia et al. Costs of rheumatoid arthritis in France: a multicenterstudy of 1109 patients managed by hospital-based rheumatologists. J Rheumatol, 31 (2004), pp. 1297–1304

[9] F. Xie. The need for standardization: a literature review of indirect costs of rheumatoid arthritis and osteoarthritis. Arthritis Rheum, 59 (2008), pp. 1027–1033

[10] L.C. Franke, A.J. Ament, M.A. van de Laar, A. Boonen, J.L. Severens. Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol, 27 (2009), pp. S118–S123

[11] B. Fautrel, S.M.M. Vertappen, A. Bonnen. Economic consequences and potential benefits. Best Pract Res Clin Rheumatol, 27 (2011), pp. 607–624

[12] A. Boonen, J.L. Severens. The burden of illness of rheumatoid arthritis. Clin Rheumatol, 30 (Suppl. 1) (Mar 2011), pp. S3–S8

[13] G. Kobelt, A.S. Woronoff, B. Richard, P. Peeters, J. Sany. Disease status, costs and quality of life of patients with rheumatoid arthritis in France: the ECO-PR Study Joint Bone Spine, 75 (2008), pp. 408–415

[14] A. Beresniak, L. Gossec, P. Goupille, A. Saraux, M. Bamberger, B. Bregman et al. Direct cost-modeling of rheumatoid arthritis according to disease activity categories in France. J Rheumatol, 38 (3) (Mar 2011), pp. 439–445

[15] G.S. Metsios, A. Stavropoulos-Kalinoglou, G.J. Treharne, A.M. Nevill, A. Sandoo, V.F. Panoulas et al. Disease activity and low physical activity associate with number of hospital admissions and length of hospitalisation in patients with rheumatoid arthritis. Arthritis Res Ther, 13 (3) (Jun 29 2011), p. R108

[16]R. Tuominen, M. Azbel, J. Hemmilä, T. Möttönen. Willingness to pay for improvement of physical function among rheumatoid arthritis patients as measured by Health Assessment Questionnaire. Rheumatol Int, 31 (3) (Mar 2011), pp. 347–352

[17] K. Puolakka, H. Kautiainen, T. Mottonen, P. Hannonen, M. Korpela, M. Hakala et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recent-onset rheumatoid arthritis. Scand J Rheumatol, 38 (2) (Mar-Apr 2009), pp. 96–103

[18]G. Kobelt, P. Lindgren, Geborek. Costs and outcomes for patients with rheumatoid arthritis treated with biological drugs in Sweden: a model based on registry data. Scand J Rheumatol, 38 (6) (Nov-Dec 2009), pp. 409–418

[19]K. Michaud, J. Messer, H.K. Choi, F. Wolfe. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum, 48 (10) (Oct 2003), pp. 2750–2762

[20] F. Wolfe, K. Michaud. Predicting depression in rheumatoid arthritis: the signal importance of pain extent and fatigue, and comorbidity. Arthritis Rheum, 61 (2009), pp. 667–673

[21] H. Radner, J.S. Smolen, D. Aletaha. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis, 69 (2010), pp. 536–541

[22] A.T. Joyce, P. Smith, R. Khandker, J.M. Melin, A. Singh. Hidden cost of rheumatoid arthritis (RA): estimating cost of comorbid cardiovascular disease and depression among patients with RA. J Rheumatol, 36 (2009), pp. 743–752

[23] F. Wolfe, K. Michaud. Out-of-pocket expenses and their burden in patients with rheumatoid arthritis.Arthritis Rheum, 61 (2009), pp. 1563–1570

[24] R. Geletka, E.W. St Clair. Treatment of early rheumatoid arthritisBest Pract Res Clin Rheumatol, 17 (5) (Oct 2003), pp. 791–809

[25] A. Finckh, N. Bansback, C.A. Marra, A.H. Anis, K. Michaud, S. Lubin et al.Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. Ann Intern Med, 151 (9) (Nov 3 2009), pp. 612–621

[26] B.H. Resman-Targoff, M.P. Cicero. Aggressive treatment of early rheumatoid arthritis: recognizing the window of opportunity and treating to target goals. Am J Manag Care, 16 (9 Suppl.) (Nov 2010), p. S249-

[27]M.G. Feely, J.R. O'Dell.Update on the use of conventional disease-modifying antirheumatic drugs in the management of rheumatoid arthritis. Curr Opin Rheumatol, 22 (3) (May 2010), pp. 316–320

[28]S.K. Agarwal. Biologic agents in rheumatoid arthritis: an update for managed care professionals. J Manag Care Pharm, 17 (9 Suppl. B) (Nov-Dec 2011), pp. S14–S18 [Review]

[29] F. Breedveld. The value of early intervention in RA—a window of opportunity.Clin Rheumatol, 30 (Suppl. 1) (Mar 2011), pp. S33–S39

[30]B. Svensson, A. Boonen, K. Albertsson, D. van der Heijde, C. Keller, I. Hafström. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum, 52 (11) (Nov 2005), pp. 3360–3370

[31]J.R. Kirwan, J.W. Bijlsma, M. Boers, B.J. Shea. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev (1) (Jan 24 2007), p. CD006356

[32] S.L. Gorter, J.W. Bijlsma, M. Cutolo, J. Gomez-Reino, M. Kouloumas, J.S. Smolen et al.Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis, 69 (6) (2010 Jun), pp. 1010–1014

[33] M. Boers. The COBRA trial 20 years later. Clin Exp Rheumatol, 29 (5 Suppl. 68) (Sep–Oct 2011), pp. S46–S51

[34] S.M. Naguwa. Tumor necrosis factor inhibitor therapy for rheumatoid arthritis. Ann N Y Acad Sci, 1051 (Jun 2005), pp. 709–715

[35] Y.-F. Chen, P. Jobanputra, P. Barton, S. Jowett, S. Bryan, W. Clark et al.A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess, 10 (42) (2006), pp. iii–xiii [1–247]

[36] H. Castro-Rueda, A. Kavanaugh. Therapy for early rheumatoid arthritis: the latest evidence. Curr Opin Rheumatol, 20 (3) (May 2008), pp. 314–319

[37]W.B. van den Hout, Y.P. Goekoop-Ruiterman, C.F. Allaart, J.K. de Vries-Bouwstra, J.M. Hazes, P.J. Kerstens et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum, 61 (2009), pp. 291–299

[38] M.T. Nurmohamed, B.A. Dijkmans. Efficacy, tolerability and cost effectiveness of disease-modifying antirheumatic drugs and biologic agents in rheumatoid arthritis. Drugs, 65 (5) (2005), pp. 661–694

[39]G. Van Der Velde, B. Pham, M. Machado, L. Ieraci, W. Witteman, C. Bombardier et al. Cost-effectiveness of biologic response modifiers compared to disease-modifying antirheumatic drugs for rheumatoid arthritis: a systematic review. Arthritis Care Res, 1 (63) (2011), pp. 65–78

[40] N.J. Bansback, D.A. Regier, R. Ara, A. Brennan, K. Shojania, J.M. Esdaile et al. An overview of economic evaluations for drugs used in rheumatoid arthritis: focus on tumour necrosis factor-alpha antagonists. Drugs, 65 (4) (2005), pp. 473–496

[41]Q.V. Doan, C.F. Chiou, R.W. Dubois. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. J Manag Care Pharm, 12 (7) (2006), pp. 555–569

[42]M. Schoels, J. Wong, D.L. Scott, A. Zink, P. Richards, R. Landewé et al.Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis, 69 (6) (Jun 2010), pp. 995–1003

[43] K. Malottki, P. Barton, A. Tsourapas, A.O. Uthman, Z. Liu, K. Routh et al. 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 Technol Assess, 15 (2011), pp. 1–278

[44]P.D. Kiely, C. Deighton, J. Dixey, A.J. Östör, on behalf of the British Society for Rheumatology Standards, Guidelines and Audit Working Group Biologic agents for rheumatoid arthritis—negotiating the NICE technology appraisals Rheumatology, 51 (2012), pp. 24–31

[45] M.A. Cimmino, G. Leardini, F. Salaffi, M. Intorcia, A. Bellatreccia, D. Dupont et al.Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in Italy: a modelling approach. Clin Exp Rheumatol, 29 (4) (Jul-Aug 2011), pp. 633–641

[46]S. Merkesdal, T. Kirchhoff, D. Wolka, G. Ladinek, A. Kielhorn, A. Rubbert-Roth. Cost-effectiveness analysis of rituximab treatment in patients in Germany with rheumatoid arthritis after etanercept-failure. Eur J Health Econ, 11 (1) (Feb 2010), pp. 95–104

[47] A. Kielhorn, D. Porter, A. Diamantopoulos, G. Lewis. UK cost–utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin, 24 (9) (Sep 2008), pp. 2639–2650

[48]T.A. Hallinen, E.J. Soini, K. Eklund, K. Puolakka. Cost–utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. Rheumatology (Oxford), 49 (4) (Apr 2010), pp. 767–777

[49] A. Diamantopoulos, M. Benucci, S. Capri, W. Berger, N. Wintfeld, G. Giuliani et al. Economic evaluation of tocilizumab combination in the treatment of moderate-to-severe rheumatoid arthritis in Italy. J Med Econ, 15 (3) (2012), pp. 576–585

[50] J.S. Smolen, R. Landewé, F.C. Breedveld, M. Dougados, P. Emery, C. Gaujoux-Viala et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis, 69 (6) (Jun 2010), pp. 964–975

[51]N.B. Klarenbeek, S.M. van der Kooij, M. Güler-Yüksel, J.H. van Groenendael, K.H. Han, P.J. Kerstens et al. Discontinuing treatment in patients with rheumatoid arthritis in sustained clinical remission: exploratory analyses from the BeSt study. Ann Rheum Dis, 70 (2) (Feb 2011), pp. 315–319

[52] A. Migliore, E. Bizzi, U. Massafra, F. Vacca, L.S. Martin Martin, C. Ferlito et al. A new chance to maintain remission induced by anti-TNF agents in rheumatoid arthritis patients: CYnAR study II of a 12-month follow-up. Int J Immunopathol Pharmacol, 24 (1) (Jan-Mar 2011), pp. 167–174

[53] P.P. Sfikakis. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. Curr Dir Autoimmun, 11 (2010), pp. 180–210

[54] K.L. Hyrich, K.D. Watson, A.J. Silman, D.P. Symmons, British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford), 45 (12) (Dec 2006), pp. 1558–1565

[55] L. Mancarella, F. Bobbio-Pallavicini, F. Ceccarelli, P.C. Falappone, A. Ferrante, D. Malesci et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol, 34 (8) (Aug 2007), pp. 1670–1673

[56] L.E. Kristensen, M.C. Kapetanovic, A. Gülfe, M. Söderlin, T. Saxne, P. Geborek. 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), 47 (4) (Apr 2008), pp. 495–499

[57] V. Rantalaiho, M. Korpela, L. Laasonen, H. Kautiainen, S. Järvenpää, P. Hannonen et al. Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. Arthritis Res Ther, 12 (3) (2010), p. R122

[58] L.G. Schipper, L.T. van Hulst, R. van Grol, P.L. Riel, M.E. Hulscher, J. Fransen. Meta-analysis of tight control strategies in rheumatoid arthritis: protocolized treatment has additional value with respect to the clinical outcome. Rheumatology, 49 (2010), pp. 2154–2164

[59] L.G. Schipper, M. Vermeer, H.H. Kuper, M.O. Hoekstra, C.J. Haagsma, A.A. Broeder et al. A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. Ann Rheum Dis, 71 (6) (2012), pp. 845–850

[60] E. da Silva, M.F. Doran, C.S. Crowson, W.M. O'Fallon, E.L. Matteson. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. Arthritis Rheum, 49 (2) (Apr 15 2003), pp. 216–220

[61] S. Momohara, S. Tanaka, H. Nakamura, J. Mibe, T. Iwamoto, K. Ikari et al. Recent trends in orthopedic surgery performed in Japan for rheumatoid arthritis. Mod Rheumatol, 21 (4) (Aug 2011), pp. 337–342

[62] A. Sebba. Tocilizumab: the first interleukin-6-receptor inhibitor. Am J Health Syst Pharm, 65 (15) (Aug 1 2008), pp. 1413–1418

[63] E. Terpos, K. Fragiadaki, M. Konsta, C. Bratengeier, A. Papatheodorou, P.P. Sfikakis. Early effects of IL-6 receptor inhibition on bone homeostasis: a pilot study in women with rheumatoid arthritis. Clin Exp Rheumatol, 29 (6) (Nov–Dec 2011), pp. 921–925

[64] E.C. Keystone, J.R. Curtis, R.M. Fleischmann, D.E. Furst, D. Khanna, J.S. Smolen et al. Rapid improvement in the signs and symptoms of rheumatoid arthritis following certolizumabpegol treatment predicts better longterm outcomes: post-hoc analysis of a randomized controlled trial. J Rheumatol, 38 (6) (Jun 2011), pp. 990–996

[65] J.R. Curtis, K. Luijtens, A. Kavanaugh. Predicting future response to certolizumabpegol in rheumatoid arthritis patients: Features at 12 weeks associated with low disease activity at 1 year. Arthritis Care Res (Hoboken), 64 (5) (May 2012), pp. 658–667

[66] X. Mariette, J.E. Gottenberg, P. Ravaud, B. Combe. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. Rheumatology (Oxford), 50 (1) (Jan 2011), pp. 222–229

[67] J.B. Galloway, K.L. Hyrich, L.K. Mercer, W.G. Dixon, B. Fu, A.P. Ustianowski et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford), 50 (1) (Jan 2011), pp. 124–131

[68] F. Wolfe, L. Caplan, K. Michaud. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum, 54 (2) (Feb 2006), pp. 628–634

[69] F. Atzeni, P. Sarzi-Puttini, C. Botsios, A. Carletto, P. Cipriani, E.G. Favalli et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev, 12 (2) (2012), pp. 225–229