

Original article

Effectiveness and long-term retention of anti-tumour necrosis factor treatment in juvenile and adult patients with juvenile idiopathic arthritis: data from Reuma.pt

Ana F. Mourão^{1,2,3}, Maria J. Santos^{1,4}, José A. Melo Gomes⁵,
Fernando M. Martins^{1,6}, Sílvia C. Mendonça⁶, Filipa Oliveira Ramos⁷,
Susana Fernandes⁵, Manuel Salgado⁸, Margarida Guedes⁹, Sónia Carvalho¹⁰,
José A. Costa¹¹, Iva Brito^{12,13}, Cátia Duarte¹⁴, Carolina Furtado¹⁵, Ana Lopes¹,
Ana Rodrigues^{1,16}, Graça Sequeira¹⁷, Jaime C. Branco^{2,3}, João E. Fonseca^{1,7} and
Helena Canhão^{1,7}

Abstract

Objectives. Assess the effectiveness and safety of biologic therapy as well as predictors of response at 1 year of therapy, retention rate in biologic treatment and predictors of drug discontinuation in JIA patients in the Portuguese register of rheumatic diseases.

Methods. We prospectively collected patient and disease characteristics from patients with JIA who started biological therapy. Adverse events were collected during the follow-up period. Predictors of response at 1 year and drug retention rates were assessed at 4 years of treatment for the first biologic agent.

Results. A total of 812 JIA patients [65% females, mean age at JIA onset 6.9 years (s.d. 4.7)], 227 received biologic therapy; 205 patients (90.3%) were treated with an anti-TNF as the first biologic. All the parameters used to evaluate disease activity, namely number of active joints, ESR and Childhood HAQ/HAQ, decreased significantly at 6 months and 1 year of treatment. The mean reduction in Juvenile Disease Activity Score 10 (JADAS10) after 1 year of treatment was 10.4 (s.d. 7.4). According to the definition of improvement using the JADAS10 score, 83.3% respond to biologic therapy after 1 year. Fourteen patients discontinued biologic therapies due to adverse events. Retention rates were 92.9% at 1 year, 85.5% at 2 years, 78.4% at 3 years and 68.1% at 4 years of treatment. Among all JIA subtypes, only concomitant therapy with corticosteroids was found to be univariately associated with withdrawal of biologic treatment ($P = 0.016$).

Conclusion. Biologic therapies seem effective and safe in patients with JIA. In addition, the retention rates for the first biologic agent are high throughout 4 years.

Key words: juvenile idiopathic arthritis, efficacy, safety, biological treatment.

¹Rheumatology Research Unit, Instituto de Medicina Molecular, Lisboa Ocidental, ²CEDOC, Faculdade de Ciências Médicas da Universidade Nova de Lisboa, Lisboa, ³Rheumatology Department, Hospital Garcia de Orta, Almada, ⁴Instituto Português de Reumatologia, ⁵Portuguese Society of Rheumatology, ⁶Rheumatology Department, Lisbon Academic Medical Center, Lisbon, ⁷Pediatrics Department, Centro Universitário Hospitalar de Coimbra, Coimbra, ⁸Pediatrics Department, Unidade de Imunologia Clínica, Centro Hospitalar do Porto, Porto, ⁹Pediatrics Department, Centro Hospitalar do Médio-Ave, Famalicão, ¹⁰Rheumatology Department, ULSAM – Hospital Conde de Bertiandos, Ponte de Lima, ¹¹Rheumatology Department, Hospital de São João, ¹²Faculdade de

Medicina da Universidade do Porto, Porto, ¹⁴Rheumatology Department, Centro Universitário Hospitalar de Coimbra, Coimbra, ¹⁵Rheumatology Department, Hospital do Divino Espírito Santo, S. Miguel, Açores, ¹⁶Rheumatology Department, Hospital de Santo Espírito, Angra do Heroísmo, Terceira and ¹⁷Rheumatology Department, Centro Hospitalar do Algarve, Faro, Portugal

Submitted 16 February 2015; revised version accepted 2 November 2015

Correspondence to: Ana F. Mourão, Rheumatology Research Unit, Instituto de Medicina Molecular, Avenida Professor Egas Moniz, Edifício Egas Moniz, 1649-028 Lisbon, Portugal.
E-mail: afilipamourao@gmail.com

Rheumatology key messages

- Our data from Reuma.pt suggest that biologic therapies seem effective and safe in patients with JIA.
- The majority of patients with JIA respond to therapy after 1 year of biologic treatment.
- Long-term retention in biologic treatment is high in JIA patients.

Introduction

JIA is the most common rheumatic disease of childhood, affecting 1/1000 children, and includes a heterogeneous group of chronic arthritis of unknown aetiology that begins before 16 years of age. According to disease onset, seven categories can be identified [1].

The management of JIA has traditionally been modelled on the RA treatment strategy, with MTX and, more recently, biologic medications forming the mainstay of therapy [2–6]. When inflammatory activity is not controlled with MTX or if MTX is not tolerated, the next therapeutic step is usually the addition of a TNF inhibitor (with the exception of systemic JIA), either alone or in combination with MTX [7]. However, JIA is an umbrella term for a group of childhood-onset arthritides, many of which are quite different from RA. Knowing that the JIA ILAR categories represent, in fact, different diseases, the response to anti-TNF therapies may also differ according to the subtype of the disease. To date, there are currently five biologics licensed for the treatment of JIA: etanercept, abatacept, adalimumab, tocilizumab and canakinumab. Other biologic options are under evaluation and some are often prescribed off-label.

Large registries played a crucial role in analysing the effectiveness and long-term safety of biologic treatments in JIA [8–11]. However, little information is available from registries that include JIA patients starting biologics at any age, including adulthood. Moreover, data on predictors of response to biologic therapy and long-term retention rates are scarce.

In 2008, the Portuguese Society of Rheumatology developed an observational registry of patients with rheumatic diseases, including JIA, the Portuguese Register of Rheumatic Diseases (Reuma.pt) [12]. In 2012, national recommendations for the use of biologic therapies in children and adolescents with JIA were updated, supporting physicians in their therapeutic decisions [13]. The use of biologic therapy in Portugal is limited to those patients who are either intolerant to MTX and/or have arthritis activity that is not controlled by MTX [13].

This study aims to assess the effectiveness of the first biologic therapy at 6 months and 1 year of treatment as well as safety during the overall follow-up period in JIA patients registered in Reuma.pt. Our secondary objectives were to study the predictive factors of response to treatment at 1 year, the retention rate at 4 years of biologic treatment and the factors associated with biologic drug withdrawal in the treatment of JIA.

Methods

Our study was based on Reuma.pt, which includes JIA patients receiving biologic therapies and synthetic

DMARDs. Our study was approved by the scientific committee of Reuma.pt. Reuma.pt is approved by the National Commission for Data Protection. All patients fulfilled the ILAR criteria for the classification of JIA [1].

We analysed all patients with a diagnosis of JIA registered in Reuma.pt until September 2013, irrespective of age at entry into the cohort (patients who started biologic therapy in adulthood were also included). At the start of biologic treatment (baseline), we collected the following data: age, gender, JIA category, age at JIA onset, disease duration, number of active joints, patient's pain visual analogue scale (VAS), patient's disease global activity VAS, physician's global disease activity VAS, extra-articular manifestations, Childhood HAQ (CHAQ) or HAQ (as appropriate) [14], ESR, CRP and concomitant therapy with DMARDs and/or corticosteroids. Follow-up data were considered during the first biologic therapy.

Follow-up data for effectiveness (disease activity) were obtained at 6 months and 1 year after starting the first biologic and included the number of active joints, ESR and CHAQ/HAQ. To calculate response to treatment we used the delta Juvenile Disease Activity Score (JADAS), a recent composite score found to be a valid instrument for assessment of disease activity in JIA [15] and, in addition, the definition of improvement using the JADAS10 [16]. According to this new definition of improvement using the JADAS [16], if the JADAS10 baseline was between 5 and 15 (low disease activity), there is a response to therapy if delta JADAS is >4 ; if the JADAS10 baseline is between 15 and 25 (moderate disease activity), there is a response to therapy if delta JADAS is >10 ; and if the JADAS10 baseline is between 25 and 40 (high disease activity), there is a response to therapy if delta JADAS is >17 . Safety analysis (severe adverse events) was performed with the cumulative events at the end of the follow-up. Retention rates for the first biologic were calculated yearly in the first 4 years of treatment. The reason for biologic withdrawal was also collected.

Statistical analysis

Each patient contributed data regarding the course of their first biologic treatment only.

In order to study retention rates, we included only patients with follow-up periods of at least 1 year. Drug retention rates were calculated using the Kaplan–Meier method.

The Cox regression model was used to identify predictors of drug discontinuation until 4 years, so patients were censored at the time of last consultation or at 4 years of treatment, whichever came first. At first, crude hazard ratios were obtained using all JIA categories combined. Subsequently the analysis was repeated using only patients with polyarthritis (polyarticular RF positive, polyarticular RF negative and extended oligoarticular JIA). The

proportional hazards assumption was verified. As a secondary analysis, we repeated all of the main analyses using only the patients that started biologic treatment before the age of 18 years. Statistical analysis was made in R version 2.15.3 (R Project for Statistical Computing, Vienna, Austria) [17].

Results

Twenty-one centres and 77 clinicians across the country contributed data for this study. Of the 812 patients with JIA registered in Reuma.pt [mean age 19.9 years (s.d. 11.3), 65% females, mean age at JIA onset 6.9 years (s.d. 4.7)], 227 received biologic therapy and the median duration of the first biologic agent treatment was 4.5 years [interquartile range (IQR) 2.2–5.9] (the characteristics of the patients treated with biologic agents are presented in Table 1). The mean age at disease onset of JIA patients ever treated with biologic DMARDs was 7.5 years (s.d. 4.9; IQR 0.8–11.6) and the mean age for starting biologic therapy was 16.2 years (s.d. 9.4; IQR 1.8–20.4). Sixty-nine (30.4%) patients started biologic therapy in adulthood.

Most patients (90.3%) were treated with anti-TNF as a first line treatment: etanercept 69.2% (157 patients), adalimumab 12.8% (29 patients) and infliximab 8.4% (19 patients). All patients taking anakinra (4.8%) had systemic JIA (Table 2). During the follow-up, 32 (14.1%) patients switched biologic treatment once, 13 (5.7%) patients switched twice, 2 (0.9%) switched three times, 3 (1.3%) patients switched four times and 1 (0.4%) patient switched five times.

Twenty-eight patients had uveitis and 10 of them were treated with infliximab.

In the subgroup of patients who started biologic therapy as adults (30.4%), there was a greater proportion of female patients (76.8% vs 59.5%, $P=0.02$), older age at JIA onset [9.5 years (s.d. 5.3) vs 6.6 (s.d. 4.5), $P<0.0001$] and longer overall disease duration [24.4 years (s.d. 11.3) vs 9.5 (s.d. 5.3), $P<0.0001$] compared with those who started in childhood. The proportion of each category of JIA in the two subgroups was similar, as well as the distribution of the first biologic agent used.

Effectiveness of biologic treatment

All the parameters used to evaluate disease activity, namely the number of active joints, ESR and CHAQ/HAQ, decreased significantly at 6 months and 1 year of treatment with biologic agents. The mean active joint count reported at the beginning of biologic therapies was 5.1 (s.d. 5.8) and decreased to 1.2 (s.d. 2.4; $P<0.0001$) and 1.0 (s.d. 3.1; $P<0.0001$) after 6 months and 1 year of therapy, respectively (Fig. 1A). Mean ESR was 33.9 mm/first hour (s.d. 25.3) at biologic treatment start and was of 22.0 (s.d. 24.0; $P<0.001$) and 19.1 (s.d. 18.0; $P<0.0001$) after 6 months and 1 year of treatment, respectively (Fig. 1B). The mean CHAQ/HAQ decreased from 0.8 (s.d. 0.7) at baseline to 0.4 (s.d. 0.5; $P<0.0001$) at 6 months and 0.4 (s.d. 0.5; $P<0.0001$) at 1 year (Fig. 1C). In accordance, the mean CRP was 2.4 mg/dl (s.d. 3.7) at biologic treatment start and of

TABLE 1 Characteristics of JIA patients treated with biologic agents

	Patients ever treated with biologic agents
Total number of patients	227
Gender, female/male, n (%) / n (%)	147 (64.8)/80(35.2)
Age at disease onset, mean (s.d.), years	7.5 (4.9)
Disease duration, mean (s.d.), years	13.7 (10.1)
JIA categories fulfilled, n	206
JIA category not stated, n	21
Persistent oligoarticular, n (%)	20 (9.7)
Extended oligoarticular, n (%)	33 (16)
Polyarticular RF positive, n (%)	36 (17.5)
Polyarticular RF negative, n (%)	48 (23.3)
Systemic, n (%)	28 (13.6)
Enthesitis-related arthritis, n (%)	31 (15.1)
Psoriatic arthritis, n (%)	10 (4.8)
Unclassified, n	0

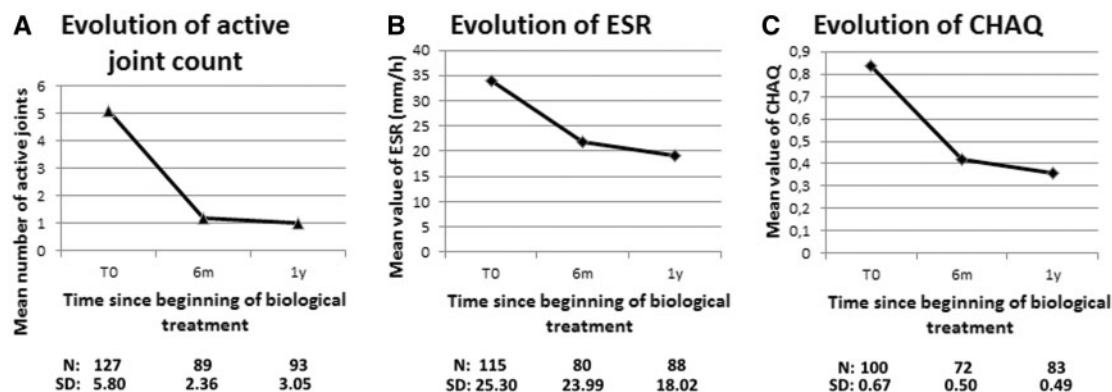
TABLE 2 Patient ($N=227$) and disease characteristics treated with biologic agents

Characteristic	Value
Age, mean (s.d.), years	16.2 (9.4)
Total amount of biologic treatment exposure, mean (s.d.), years	4.5 (3.1)
Concomitant DMARD therapy, n (%)	181 (79.7)
Methotrexate	170 (93.9)
Sulfasalazine	16 (8.8)
Other DMARDs	11 (6.1)
First biologic treatment, n (%)	227 (100)
Etanercept	157 (69.2)
Adalimumab	29 (12.8)
Abatacept	8 (3.5)
Tocilizumab	2 (0.9)
Anakinra	11 (4.8)
Infliximab	19 (8.4)
Rituximab	1 (0.4)

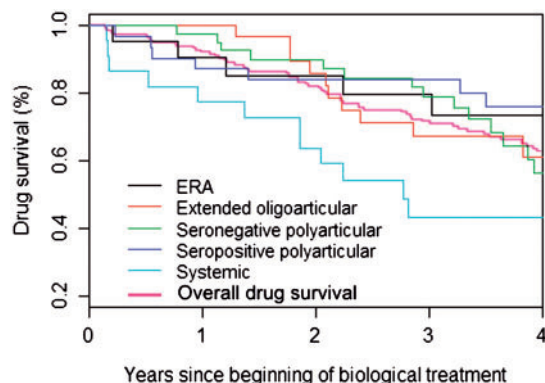
1.2 (s.d. 3.3) at 6 months ($P=0.043$) and 0.6 (s.d. 1.1) at 1 year ($P<0.0001$). Patient global disease activity, evaluated by VAS, was 43.5 mm (s.d. 26.5) at baseline, 18.2 (s.d. 19.6) at 6 months ($P<0.0001$) and 16.3 (s.d. 17.7) at 1 year ($P<0.0001$).

Safety analysis

The total length of exposure to the first biologic agent was 706.92 patient-years and, during the follow-up period, there were 1.98 events/100 patient-years. A total of 14 clinically significant adverse events (defined by the need for biologic treatment discontinuation) were reported, including infusion reaction (one patient), respiratory and urinary infections (six patients), inflammatory bowel disease (four patients), diarrhoea (one patient), tuberculin

Fig. 1 Evolution of the disease parameters in the first year of biologic treatment

Evolution of the (A) active joint count, (B) ESR and (C) CHAQ/HAQ in the first year after the beginning of biologic treatment. CHAQ: Childhood Health Assessment Questionnaire.

Fig. 2 Drug survival on the first biologic agent (Kaplan-Meier plot)

skin test conversion (one patient) and active tuberculosis (one patient).

There were no reported deaths or malignancies during the overall follow-up period of biologic treatment, 134 treatments were stopped for the following reasons: 14 (10.5%) due to an adverse event, 60 (44.8%) due to a lack/loss of efficacy (primary or secondary failure), 13 (9.7%) due to disease remission, 2 (1.49%) were lost to follow-up, 4 (3%) refused to continue treatment and 40 (29.8%) for other reasons (not specified).

Predictors of treatment response at 1 year

The mean reduction in JADAS10 after 1 year of treatment was 10.4 (s.d. 7.4) [median 9.9 (IQR 4.8–13.7)]. According to the definition of improvement using the JADAS10 score [16], 58 individuals had registered information of the variables that allowed determining JADAS10 response at 1 year of biologic therapy: 83.7% responded to therapy at 6 months of biologic treatment and 83.3% responded to

biologic therapy after 1 year. These 58 individuals were comparable to the ones excluded regarding disease category ($P=0.397$), however, they were younger (mean age 13.5 vs 17.3 years, $P=0.013$) and more likely to be male (53% vs 30%, $P=0.002$). Due to the small number of patients and high proportion of responders, there was no possibility of calculating the predictors of response to biologic therapy using a binary outcome.

Retention rate and predictors of drug discontinuation

A total of 179 patients were followed up for >1 year after the beginning of the first biologic therapy, and the median treatment duration was 5.8 years (IQR 4.8–8.3). The retention rates with the first biologic were 92.9% (CI 88.5, 97.5) in the first year, 85.5% (CI 79.5, 91.9) in the second year, 78.4% (CI 71.4, 86.1) in the third year and 68.1% (CI 59.7, 77.7) in the fourth year of treatment (Fig. 2).

Taking all JIA categories into consideration, only concomitant therapy with systemic corticosteroids at baseline was found to be crudely associated with withdrawal of biologic treatment [hazard ratio (HR) 1.93 (95% CI 1.13, 3.29), $P=0.016$]. However, this association showed low statistical significance when adjusting for the other clinically relevant covariates [HR 1.47 (95% CI 0.64, 3.38), $P=0.362$]. We found a higher risk of biologic drug withdrawal among systemic JIA patients [HR 2.32 (95% CI 1.19, 4.52), $P=0.014$] compared with the polyarticular categories of disease. In addition, we failed to identify any predictors of drug discontinuation in the stratified analysis using the polyarticular categories of disease. We analysed separately the subgroup of patients that started biologic therapies in childhood. In these patients, the retention rates were similar to those of patients who started biologic treatment in adulthood.

Discussion

This article presents the results from the Portuguese national register in which we consecutively included all

patients with JIA treated with biologic therapies. The distribution of JIA categories in our registry is similar to those found in recently published inception cohorts [18–20]. These data prove, in a real-life setting with an unselected population, the sustained effectiveness and safety of biologic treatments in all JIA categories as highlighted by a high retention rate after 4 years of treatment. Etanercept was the most frequently used TNF inhibitor, most likely because it was the first biologic agent approved for JIA treatment [2].

There were few cases (20 patients) of persistent oligoarticular JIA treated with biologics, in agreement with the Portuguese guidelines for prescribing biologic therapy in JIA [13]. Paediatric rheumatologists often need to prescribe TNF blocking agents in oligoarticular JIA due to disabling active oligoarthritis or related to the higher prevalence of uveitis in this category. In multivariable models, uveitis was strongly and independently associated with non-biologic and biologic DMARD use. This implies that uveitis may frequently be the determining factor in the systemic treatment of children with oligoarticular JIA [18–23]. Nevertheless, there are no published sizable randomized studies of the systemic treatment of uveitis in children [24]. More research in this area is needed.

Biologic agents were safe during the overall follow-up period of treatment. Infections, particularly tuberculosis, are a concern for every physician prescribing biologic agents. In our study, and despite previous screening, there was one case of pulmonary tuberculosis associated with the use of a monoclonal antibody (adalimumab), and in one patient taking etanercept, we found a tuberculin skin test conversion that led to discontinuation of biologic therapy. Four patients were diagnosed with chronic inflammatory bowel disease (IBD) during biologic treatment, all with etanercept. Several other cases of new-onset IBD during etanercept use were reported [25–30]. The mechanism behind this effect is still unknown and more research is required in this field. We did not find any discontinuations associated with the development of psoriasis, lupus-like or other chronic inflammatory or autoimmune diseases. No cases of malignancy were observed.

We have observed a large gap between the mean age at disease onset of JIA patients ever treated with biologic agents [7.5 years (s.d. 4.9)] and the mean age for starting biologic therapy [16.2 years (s.d. 9.4)]: almost 10 years between disease onset and the beginning of biologic treatment. This could be related in part to the long disease duration of the adults with JIA starting biologics in adulthood and also to the retrospective insertion of these data in the registry, with a large proportion of patients being diagnosed before the approval of biologic therapies in national policies. Almost one-third of the patients included in this study started biologic treatment as an adult, a fact that is unusual in other JIA registries. Although innovative, we are aware that this could have introduced a bias in the results, since in patients with prolonged disease duration, the outcomes may be quite different from those of

children starting biologics far earlier in their disease evolution. Although we believe that including adults with JIA brings an added value to our registry and data, the instruments to measure disease activity in JIA have never been validated for adults, and this should be taken into account when analysing the data. More studies including adults with JIA are necessary to validate these instruments in this population.

TNF inhibitors are not always effective or universally tolerated, which may lead to switching among biologic agents. In our study, 22.5% of the patients switched biologic treatment during their disease course. This proportion is higher than the ~10% reported from biologics registries in the UK [6] and the Netherlands [31], but is lower than the ~35% reported from Finland [32] and the 28% reported in the USA [18].

Patients with JIA had a high retention rate of biologic treatment in the first 4 years of therapy: 93% remained on treatment in the first year and 68% in the first 4 years of treatment. The retention rates found in our study were similar to the JIA British cohort [6]. The prolonged use of biologic agents suggests that for the majority of patients the drug was effective and well tolerated.

Although we found a crude association between treatment withdrawal and corticosteroid use, we found this association to be at least partly confounded by the CHAQ/HAQ score at baseline. In addition, this finding was not confirmed in the polyarticular category of JIA. Thus we cannot associate with certainty concomitant therapy with systemic corticosteroids and discontinuation of biologic treatment. We also found a higher risk of drug cessation among systemic arthritis patients, and this group has been proposed previously to be associated with a poorer response to etanercept [33, 34].

This study is purely observational and the sample might not be completely representative of the JIA population since most patients [526 (65%)] were from rheumatology centres in Lisbon. We choose the JADAS10 score as our outcome measure for treatment response, although this instrument has limitations, as pointed out by its authors. Due to the small number of patients and high proportion of responders, there was no possibility of calculating the predictors of response to biologic therapy.

The lack of follow-up information on limited joint count precluded the use of the ACR Pediatric response criteria. The JADAS calculation may have had some limitations in our study population. As the authors of the JADAS point out, although the score was designed to be robust enough to cover all categories of JIA, a thorough assessment of disease activity in children with systemic JIA requires quantification of extra-articular manifestations, particularly fever and rash. Missing data and the small number of patients with available information for calculating response to treatment limited the use of multivariate models and stratified analyses by disease category. Because laboratory tests are frequently missing, in accordance with McErlane *et al.* [35], our group also tested the JADAS with and without ESR [36]. The correlation between the JADAS with ESR and JADAS without ESR (clinical JADAS

or three-variable JADAS) was high ($r=0.97$, $P=0.0001$), indicating that when ESR is not available, the JADAS can be calculated without this variable, allowing the measurement of disease activity anytime and anywhere. Another limitation concerns the decision to report an adverse event, which is up to the treating physician, and physicians probably reported only the clinically relevant ones, which might have led to underreporting compared with controlled clinical trials.

Conclusion

Our data from Reuma.pt reinforce that biologic therapies seem effective and safe in all JIA categories. In addition, retention rates with the first biologic agent were high during the first 4 years of treatment.

Acknowledgements

A.F.M.: conceptualized and designed the study; participated in the acquisition, analysis and interpretation of data; coordinated and supervised data collection; drafted the initial and final manuscript and approved the final manuscript as submitted. M.J.S., J.E.F. and H.C.: conceptualized and designed the study, carried out the initial analyses, critically reviewed and revised the manuscript and approved the final manuscript as submitted. F.M.M., S.C.M.: carried out acquisition of the data and statistical analyses, reviewed and revised the manuscript and approved the final manuscript as submitted. J.A.M.G., F.O.R., S.F., M.S., M.G., S.C., J.A.C., I.B., C.D., C.F., A.L., A.R., G.S., J.C.B.: contributed in the acquisition of data, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: J.A.M.G. has been a scientific clinical consultant and/or member of a speaker's bureau of BMS, AbbVie, Novartis, Pfizer and Roche. All other authors have declared no conflicts of interest.

References

- Petty RE, Southwood TR, Manners P *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
- Lovell DJ, Giannini EH, Reiff A *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763–9.
- Lovell DJ, Reiff A, Ilowite NT *et al.* Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008;58:1496–504.
- Lovell DJ, Ruperto N, Goodman S *et al.* Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810–20.
- Ruperto N, Lovell DJ, Cuttica R *et al.* A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2007;56:3096–106.
- Southwood TR, Foster HE, Davidson JE *et al.* Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. *Rheumatology* 2011;50:189–95.
- Schmeling H, Mathony K, John V *et al.* A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. *Ann Rheum Dis* 2001;60:410–2.
- Davies R, Southwood TR, Kearsley-Fleet L *et al.* Medically significant infections are increased in patients with juvenile idiopathic arthritis treated with etanercept: results from the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. *Arthritis Rheumatol* 2015;67:2487–94.
- Geikowski T, Becker I, Horneff G; German BIKER Registry Collaborative Study Group. Predictors of response to etanercept in polyarticular-course juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2014;53:1245–9.
- Zuber Z, Rutkowska-Sak L, Postępski J *et al.* Etanercept treatment in juvenile idiopathic arthritis: the Polish registry. *Med Sci Monit* 2011;17:SR35–42.
- Giannini EH, Ilowite NT, Lovell DJ *et al.* Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. *Arthritis Rheum* 2009;60:2794–804.
- Canhão H, Faustino A, Martins F, Fonseca JE, on behalf of the Rheumatic Diseases Portuguese Register Board Coordination, Portuguese Society of Rheumatology. Reuma.pt: the Rheumatic Diseases Portuguese Register. *Acta Reumatol Port* 2011;36:45–56.
- Santos MJ, Canhão H, Conde M *et al.* Portuguese recommendations for the use of biological therapies in children and adolescents with juvenile idiopathic arthritis – December 2011 update. *Acta Reumatol Port* 2012;37:48–68.
- Melo-Gomes JA, Ruperto N, Canhao H *et al.* The Portuguese version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol* 2001;19:S126–30.
- Consolaro A, Ruperto N, Bazso A *et al.* Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:658–66.
- Horneff G, Becker I. Definition of improvement in juvenile idiopathic arthritis using the juvenile arthritis disease activity score. *Rheumatology (Oxford)* 2014;53:1229–34.
- R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2013. <http://www.R-project.org/>
- Beukelman T, Ringold S, Davis T *et al.* Disease modifying anti-rheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA registry. *J Rheumatol* 2012;39:1867–74.
- Hyrich KA, Lal SD, Foster HE *et al.* Disease activity and disability in children with juvenile idiopathic arthritis one year following presentation to paediatric rheumatology.

- Results from the Childhood Arthritis Prospective Study. *Rheumatology* 2010;49:116–22.
- 20 Oen K, Duffy CM, Tse SM *et al.* Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. *Arthritis Care Res* 2010;62:527–36.
 - 21 Heiligenhaus A, Niewerth M, Ganser G *et al.* Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology* 2007;46:1015–9.
 - 22 Simonini G, Cantarini L, Bresci C *et al.* Current therapeutic approaches to autoimmune chronic uveitis in children. *Autoimmun Rev* 2010;9:674–83.
 - 23 Levy-Clarke G, Jabs D, Read RW *et al.* Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology* 2014;121:785–96.
 - 24 Heiligenhaus A, Michels H, Schumacher C *et al.* Evidence-based interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. *Rheumatol Int* 2012;32:1121–33.
 - 25 Pontikaki I, Gerloni V, Gattinara M *et al.* Side effects of anti-TNF α therapy in juvenile idiopathic arthritis. *Reumatismo* 2006;58:31–8.
 - 26 Ruemmele FM, Prieur AM, Talbotec C *et al.* Development of Crohn disease during anti-TNF- α therapy in a child with juvenile idiopathic arthritis. *J Pediatr Gastroenterol Nutr* 2004;39:203–6.
 - 27 D'Haens G, Swijsen C, Noman M *et al.* Etanercept in the treatment of active refractory Crohn's disease: a single-center pilot trial. *Am J Gastroenterol* 2001;96:2564–8.
 - 28 Ardizzone S, Bianchi Porro G. Biologic therapy for inflammatory bowel disease. *Drugs* 2005;65:2253–86.
 - 29 Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. *Ann Rheum Dis* 2008;67:1145–52.
 - 30 Wiegering V, Morbach H, Dick A, Girschick HJ. Crohn's disease during etanercept therapy in juvenile idiopathic arthritis: a case report and review of the literature. *Rheumatol Int* 2010;30:801–4.
 - 31 Prince FH, Twilt M, ten Cate R *et al.* Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 2009;68:635–41.
 - 32 Tynjala P, Vahasalo P, Honkanen V *et al.* Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. *Ann Rheum Dis* 2009;68:552–7.
 - 33 Quartier P, Taupin P, Bourdeaut F *et al.* Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset subtype. *Arthritis Rheum* 2003;48:1093–101.
 - 34 Kimura Y, Pinho P, Walco G *et al.* Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. *J Rheumatol* 2005;32:935–42.
 - 35 McErlane F, Beresford MW, Baildam EM *et al.* Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. *Ann Rheum Dis* 2013;72:1983–8.
 - 36 Mourão AF, Santos MJ, Melo-Gomes J *et al.* Using the Juvenile Arthritis Disease Activity Score based on erythrocyte sedimentation rate or C-reactive protein level: results from the Portuguese register. *Arthritis Care Res (Hoboken)* 2014;66:585–91.