BIOLOGIC THERAPY IN RHEUMATOID ARTHRITIS: RESULTS FROM THE ROMANIAN REGISTRY OF RHEUMATIC DISEASES ONE YEAR AFTER INITIATION

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Abstract

The extensive use of biologics in the treatment of rheumatoid arthritis (RA) has called for a long-term evaluation of the efficacy and safety of this therapy. Patient registries are currently used to provide real-life information on long-term efficacy and safety of biologics, thus overcoming limitations imposed by methodologies of clinical studies. Limited data are available from registries in Central and Eastern Europe.

"The Romanian Registry of Rheumatic Diseases" (RRBR) is an electronic application that includes data of all RA patients treated with biologics in Romania. This observational, prospective study initiated in February 2013, collected multiple variables: demographics, RA therapies, disease activity, adverse events, in order to provide data for RA patients in our country.

This is the first published report presenting data for 4499 RA patients treated with biologics included in the RRBR. The average age of participants is 57.70 years, 85.3% are women, with a mean disease duration of 12.62 years. 58.45% of the patients are treated with a tumour necrosis factor (TNF) alpha inhibitors and 41.55% with Rituximab. Six months after initiating a biologic therapy, delta DAS28 dropped by 3.29; 41.1% of the patients who continued therapy maintained remission (mean DAS28 = 2.58). Only 473 adverse events were recorded, mostly infections. Nevertheless, safety data are insufficient due to poor reporting of adverse effects.

Rezumat

Utilizarea agenților biologici în poliartrita reumatoidă (PR) a impus necesitatea evaluării pe termen lung a eficienței și siguranței acestor terapii. Registrele de pacienți sunt folosite frecvent pentru a furniza informații din practica medicală, fără constrângerile criteriilor restrictive din studiile clinice. Datele provenite din registrele din Centrul și Estul Europei sunt încă extrem de limitate.

"Registrul Român de Boli Reumatice" (RRBR) este o aplicație informatică ce include toți pacienții cu PR din România tratați cu medicamente biologice. Acest studiu observațional, prospectiv lansat în februarie 2013, a colectat multiple

variabile: demografice, terapiile biologice, indici de activitate, evenimente adverse, în scopul obținerii de date specifice pacienților cu RA din România.

Acesta este primul raport publicat prezentând datele pentru 4499 pacienți tratați cu agenți biologici incluși în RRBR. Vârsta medie a participanților este 57,70 ani, 85,3% sunt femei, cu o durată medie a bolii de 12,62 ani; 58,45% urmează tratament TNF alfa inhibitori, iar 41,55% cu RTX. În primele 6 luni de terapie biologică, delta DAS28 a scăzut cu 3,29; 41,1% dintre pacienții care continuă terapia mențin remisiunea bolii (media DAS28 = 2,58). S-au inregistrat 473 evenimente adverse, cel mai frecvent, infecții. Datele privind siguranța terapiei sunt insuficiente, prin raportarea deficitară a evenimentelor adverse.

Keywords: rheumatoid arthritis, biologic therapy, patient registry

Introduction

The introduction of biological agents in the treatment of rheumatoid arthritis (RA), has generated the necessity of an evaluation of the long-term efficacy and safety of these therapies. In addition to data from clinical trials, patient registries have been established to provide real-life information on RA patients and the outcome of therapies used in clinical practice. These instruments have been extensively used in research, due to the assumption that they are complex tools for evaluating the efficacy and tolerability of biological therapies. The registry records of patients provide significant data applicable to an unselected population of patients with RA. Information collected includes composite indexes, evaluation of effectiveness and adverse events (e.g. data on fertility, morbidity and mortality). Until recently, only two Central and Eastern Europe countries have provided reports from registries: ATTRA (Registry of patients treated with biologic TNF alpha blockers - Czech Republic) and NARRAS (RA register in Serbia) [7].

Materials and Methods

"The Romanian Registry of Rheumatic Diseases" (RRBR) is a computerized application that includes all patients with RA treated with biologics in Romania. The application belongs to the Association "Romanian Registry of Rheumatic Diseases", a non-profit organization initiated by the Romanian Society of Rheumatology, and was released in February 2013. Data are entered in the Registry by the treating rheumatologist, after the patient signs an informed consent form. The study has an observational prospective design and the aim is to provide representative data for the RA population treated with biologics in Romania (Table I).

Table I.
Variables collected from the RRBR

Demography	Disease treatment (including synthetic DMARDs)
Co-morbidities	Imaging (optional): plain X-rays, US, MRI
RA history	Utility (EQ-5D) and disability indicators (HAQ)
Joint surgery	Resource utilization: for direct costs (hospitalization,
Pulmonary/hepatic diseases	medical visits to GP and rheumatologist, for indirect costs
RA activity (DAS28 score)	(work productivity, absenteeism – medical sick-leave)
Laboratory tests	Adverse events

RRBR = The Romanian Registry of Rheumatic Diseases; DMARDs = disease modifying antirheumatic drugs; US = standard ultrasound; MRI = magnetic resonance imaging; EQ-5D = Health Related Quality of Life – five dimensions questionnaire; HAQ = Health Assessment Questionnaire; GP = general physicians.

Data were collected every 6 months, except reporting of adverse events, which had to be done at any time during evolution.

Results and Discussion

In Romania, the cost of RA biological treatment is fully reimbursed by the National Insurance House (NIH) for four biological agents: three TNF alpha blockers (Infliximab – IFX, including biosimilars; Etanercept – ETA; Adalimumab – ADA) and one anti CD20 drug (Rituximab – RTX), directed against B cells. In order to be eligible for biological treatment, a RA patient must present an active disease (defined as a DAS28 score over 5.1, including a total of at least five painful and swollen joints, a morning stiffness over 60 minutes and an increased acute phase reactant: erythrocyte sedimentation rate (ESR) > 28mm/hour or C reactive protein (CRP), quantitative assay, over 3 times the upper limit of normal) despite treatment with at least two synthetic disease modifying antirheumatic drugs (DMARDs) - mainly methotrexate, leflunomide, sulfasalazine, at maximal dosage, for at least 12 weeks each and have no contraindications for biological therapy.

Table II.
Demographic characteristics of RA patients treated with biological agents

Characteristic	**n = 4499**
Women (n, %)	3841 (85.37%)
Age, average (years)	57.70
By residence – urban (n, %)	2917 (65%)
Working status* (n, %) • Employed • Retired due to RA • Retired due to age • Not employed	 818 (18%) 1727 (38.38%) 1743 (38.74%) 18 (0.4%)

* *data missing for 193 patients*

One year after initiation (data in this report were updated at the end of June 2013), RRBR comprised a total of 4499 RA patients treated with biological agents, with the following demographic characteristics (Table II).

Based on the data provided by the NIH, the percentage of patients with RA treated with biologics in Romania is 12.6% (4499 out of 35684 RA patients undergoing treatment with synthetic DMARDs [1]. Most patients are women (85.37%), the ratio women: men being approximately 8:1, more than the gender prevalence recognized in RA [3]. A possible cause for this concentration of female patients could rely on the selection of cases with severe, active RA to be treated with biologics, which would suggest that the disease progression is more severe in women. This hypothesis however requires confirmation studies of disease prevalence by severity and sex.

The average age of RA patients treated with biologics is 57.7 years. However, 38% of the patients have permanently lost work ability due to RA and only 18% are still employed. This trend of work productivity loss, early after the diagnosis, is higher in our country compared to the literature data [6].

Figure 1 displays distribution of RA patients treated with biologics, depending on disease duration. The average duration of RA for patients on biologics is 12.62 years.

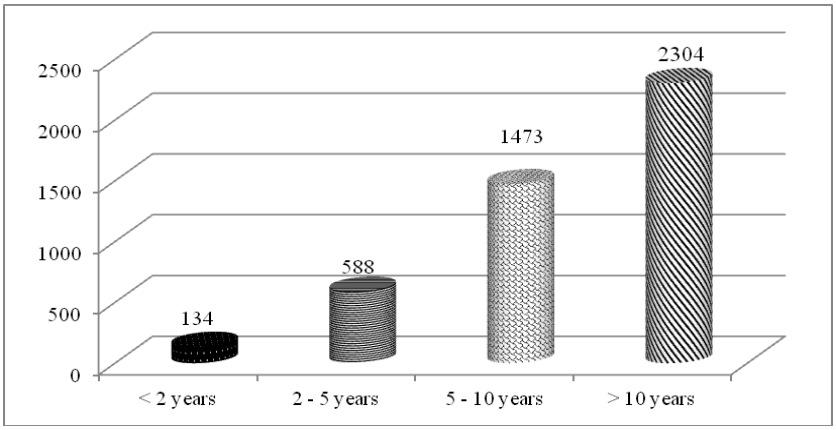

Figure 1.
Distribution of patients with RA, according to disease duration

The proportion of patients with long standing disease (>10 years disease duration) predominates in this RA group (51%) compared to patients with shorter disease duration, which raises the suspicion that the structural damage induced by RA in this group is significantly more advanced, with less chance of being favourable influenced by biologic treatments.

Biologics currently used in RA patients are shown in Figure 2.

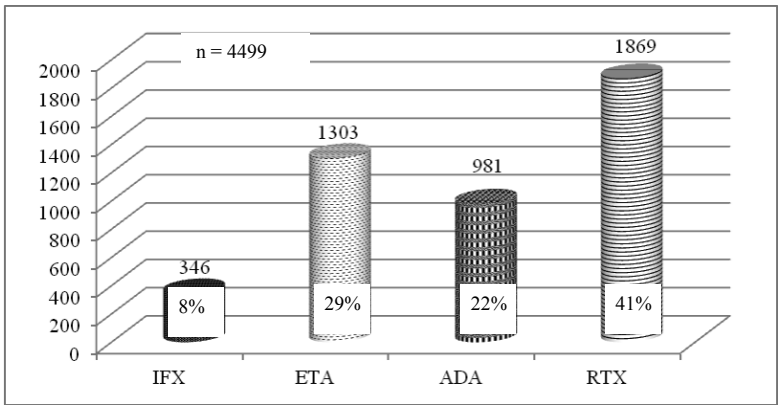

Figure 2.
Biological therapies in RRBR
Infliximab = IFX, including biosimilars; Etanercept = ETA; Adalimumab = ADA) and RTX = Rituximab.

Similarly to international guidelines applicable at that time, Romanian treatment protocols for biological therapies specify that the first biologic used in case of lack of response to synthetic DMARDs should be a TNF-alpha inhibitor ; in case of non-responders or partial responders to the first TNF alpha blocker, another TNF alpha blocker or RTX should be used [9]. Currently, the cost of other therapies is not reimbursed in Romania; hence no biologics with a different mode of action, such as tocilizumab or abatacept, are being used.

In most cases (75%) biological therapy is used associated with a synthetic DMARD, frequently methotrexate (41.29%), followed by leflunomide (31.85%) and sulfasalazine (26.41%).

The analysis of RA co-morbidities has suggested that the most commonly associated conditions are cardiovascular diseases. From the proportion of those with co-morbidities (75%, 3356 patients), the highest prevalence corresponds to high blood pressure (50.92%; 1709 cases), followed by dyslipidaemia (22.5%; 755 cases) and ischaemic heart disease (21.4%; 718 cases). This association with potential negative prognostic impact suggests that an active monitoring of cardiovascular risk in patients with RA is required.

Therapeutic efficacy is assessed by the DAS28 composite score, which is based on painful and swollen joint counts (28 joint areas), the patient's self-reported health state (on a numerical visual analogue scale from 0 to 100, where 0 means good health and 100 the worst) and an acute

phase reactant (ESR or CRP). Figure 3 displays efficacy data for the first six months of treatment for patients who have recorded in RRBR an initiation sheet, followed by a monitoring sheet after 6 months (n = 2041; 2455 files were introduced directly as monitoring, for treatments initiated before 2013 and are not included in this efficacy analysis).

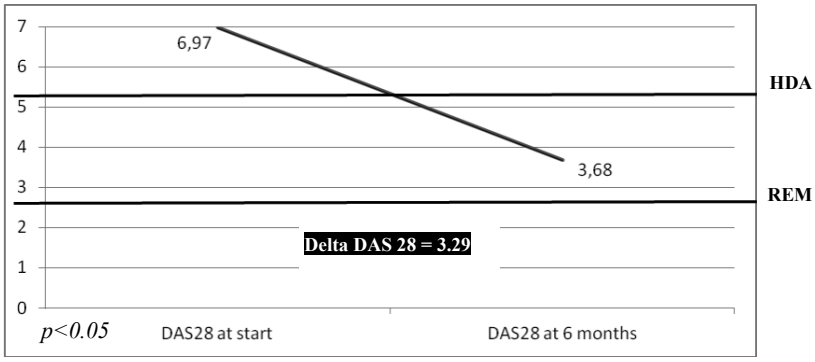

Figure 3.
Efficacy data after 6 months of treatment
HDA = high disease activity (DAS28 > 5.1); REM = remission (DAS28 < 2.6)

Efficacy assessment 6 months after initiation of TNF alpha blocker shows a decrease of DAS 28 score from a value of 6.97 (corresponding to a disease with high activity (HDA > 5.1) to a value of 3.68 (close to values defining low disease activity (LDA < 3.2), which supports the prompt therapeutic effect of biologic therapy in patients with RA.

Patients continuing a stable therapy (n = 2276), without switch, show a consolidation of therapeutic efficacy with a mean DAS28 score of 2.58, corresponding to the definition of remission (DAS28<2.6); on biological products, there were recorded the following scores: DAS28 = 2.55 (IFX); DAS 28 = 2.44 (ETA), DAS28= 2.66 (ADA) and DAS28 = 2.74 (RTX).

Analysing the dynamics of biologic therapy during 2013/2014, a number of 173 initiations were recorded, 170 switches (for non-responders or in case of adverse events), 252 treatment interruptions (54 by loss to follow-up and 198 due to adverse events) and 3901 patients are continuing the same biologic therapy.

The relatively low number of patients with a biologic therapy initiation in the last year is partly explained by a better RA management in earlier stages of disease. However, the socio-economic context in Romania cannot be overlooked as it limits health budgets, thereby putting constraints on the use of biologic therapies.

Since the launch of the RRBR, 473 adverse events (AEs) have been reported (10.52%), the majority of which (50.3%) were in accordance with those described in literature. The most common types of adverse events were infections (38%, 178), skin manifestations (22%, 104) and anaphylaxis (1%, 51) (Table III).

Table III.
Adverse events reported in RRBR

Adverse event class (n = 473 adverse events)	**Adverse event Dominant Type (n, %)**	**Comments* *6 deaths out of 473 AEs**
Infections (178, 38%)	Respiratory (106, 60%) Sepsis (3, 1.7%)	2 (3.77%) fatal 2 (67%) fatal
Skin (104, 22%)	Diffuse rash (92, 88%)	
Anaphylaxis (51, 11%)	Grade I (17, 33.5%); Grade II (22, 43%); Grade III (12, 23.5%)	
TB (15, 3.2%): *IFX = 1 (1.5%); ETA = 5 (3.8%); ADA = 5 (6.3%); RTX = 4 (3%)*	Pulmonary (14, 93.3%) Extra-pulmonary (1, 6.7%)	1 (6.7%) continue biologic treatment
Solid tumors (6, 1.23%)	Breast 3(50%); Rectal 1(16.6%) CNS 1 (16.6%); Kidney 1(16.6%)	No fatal evolution
Lymphomas (2, 0.42%)	Malignant 2 (100%)	Non-fatal
CV events (9, 1.9%)	Stroke 4 (45%) Cardiac failure 5 (55%)	1 (25%) fatal 1 (20%) fatal
Pregnancy (2, 0.42%)	Live birth 2 (100%)	2 (100%) resume biologics

TB = tuberculosis; CV = cardiovascular; AE = adverse event; CNS = Central Nervous System.

According to the literature, infectious AEs are the most commonly observed, with a rate of 38% [4, 8]. Tuberculosis (TB) incidence consists of 15 cases, with the highest prevalence in ADA treated patients (6.3%), in concordance with the British Registry data [2]. Unlike other reports [5, 10], in the RRBR the incidence of malignancies is very low (1.23%). Nevertheless, safety data are insufficient, mainly due to poor reporting of AEs occurring during biological treatment. This artificially increases the proportion of fatal severe AEs (1.26%) *versus* the total number of recorded adverse events.

Conclusions

In addition to randomized control trials data, registries provide valuable sources of clinical data to improve treatment evaluation in the long term. Patient profile, as well as treatment efficacy and safety may be

different across countries and regions. Patient registries may provide valuable data in addition to those provided by clinical studies.

These results represent the first published report of RRBR data in terms of both efficacy and safety. Presented data confirm the efficacy of biologic therapies in RA, with an overall remission rate of 41.1% (1863) of patients treated with biologics.

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