

**EXPERT
OPINION**

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Economical aspect of biological therapy in inflammatory conditions in Hungary

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Introduction: There has been a burst in the use of biological therapies in the past decade resulting in increasing costs. In 2006 – 2010 the following biological agents were available in Hungary: adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and ustekinumab. All biological agents except rituximab were first line therapies; rituximab was a second line option in rheumatoid arthritis.

Areas covered: Data of the financing system related to health care services from the data warehouse of the Hungarian National Health Insurance Fund were in inflammatory conditions. Our analysis showed a constant increase in number of patients and overall cost of biological therapy as well as annual cost of biological agents. Distribution of first choice of biological therapy was compared in different diseases. Time from diagnosis to start of biological therapy showed relatively high deviations.

Expert opinion: In order to achieve both health benefit and cost-effectiveness it is crucial that biological therapy is initiated early enough in the course of the disease, after the failure of non-biological therapies. Health authorities in close collaboration with clinical decision-makers should ensure that early detection of the disease and early initiation of appropriate therapies—including non-biological and biological therapies—are carried out in the health care systems.

Keywords: biological therapy, cost, cost effective, inflammation, personalized therapy

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1. Introduction

The National Health Insurance Fund (NHIF) is the only health insurer operated by the Hungarian state. Funding is predominantly provided from general taxes. The cost of biological therapy is covered by the NHIF's budget of medicines (prescribed medicines), and the rate of subsidy is 100%. Indication criteria of biological therapy in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, plaque psoriasis, ulcerative colitis, and Crohn's disease covered by the NHIF are included in financing protocols. These indication criteria are as follows:

In rheumatoid arthritis (RA): disease activity score involving 28 joints, DAS28 > 5.1 over a minimum of 1-month period, inefficiency of minimum 3-month combination therapy of conventional disease modifying anti-rheumatic drugs (DMARDs)—one of the DMARDs must be methotrexate unless contraindicated, DMARD combination should be used at standard therapeutic doses unless contraindicated [1];

In ankylosing spondylitis (AS): Both ankylosing spondylitis disease activity index, BASDAI > 40 or less than 50% relative decrease in disease activity despite

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Article highlights.

- The expenses of biological therapies are affected by the relative cost of biological agents as well as the duration of therapy.
- Higher relative cost may result from increasing doses.
- In order to achieve both health benefit and cost-effectiveness it is crucial that biological therapy is initiated early enough in the course of the disease, after the failure of non-biological therapies.
- Health authorities in close collaboration with clinical decision-makers can contribute to ensuring that early detection of the disease and early initiation of proper therapies—including non-biological and biological therapies—are carried out in the health care systems.
- Personalized tailored therapy could be the most cost-effective application of biological therapies.

This box summarizes key points contained in the article.

therapy with 2 NSAIDs (minimum 1 month each) at maximal or tolerable doses [2];

In case of axial involvement in psoriatic arthritis (PsA): BASDAI > 40 or < 50% relative decrease in disease activity despite therapy with 2 NSAIDs (minimum 1 month each) in maximal or tolerable doses [3];

In case of peripheral joint involvement in PsA: DAS28 > 5.1 over a minimum of 1-month period, inefficiency of minimum 3-month therapy of 2 conventional DMARDs in combination or separately [3];

In case of serious skin involvement in PsA: psoriasis area and severity index, PASI > 15 over a minimum of 1-month period despite the 3-month therapy of 2 conventional DMARDs in combination or separately, regardless of joint status [3];

In polyarticular juvenile idiopathic arthritis (JIA): minimum five swollen joints and minimum three tender joints, elevated ESR or CRP despite corticosteroid therapy with the minimum of 0.25 mg/kg/day or 3-month therapy of methotrexate at a 15 mg/m²/week dose [4];

In plaque psoriasis (PP): PASI > 15, dermatology life quality index, DLQI > 10, body surface area, BSA > 10% (in erythrodermic or pustular form) despite the 3-month standard systemic therapy, that is, methotrexate or cyclosporine or acitretine at therapeutic doses (unless contraindicated) and PUVA (Psoralen ultraviolet A) or narrowband UVB (ultraviolet B) therapy [5].

In moderate, chronically active ulcerative colitis (UC) the indication criteria of biological therapy covered by the NHIF are: inefficiency or contraindication of conventional therapy (5-aminosalicylic acid, corticosteroid, immunosuppressant (azathioprine) at therapeutic doses unless contraindicated) or corticosteroid-dependent disease despite the use of immunosuppressant. The disease is considered corticosteroid dependent when corticosteroid dose cannot be reduced below 10 mg prednisolone (equivalent) in 3 months period without a

relapse or when relapse occurs within 3 months after reducing corticosteroid dose below 10 mg prednisolone (equivalent). Biological therapy is covered by the NHIF when severe fulminant UC does not respond to 5-day intravenous corticosteroid therapy [6].

In moderate or severe luminal Crohn's disease (CD) (Crohn's disease activity index, CDAI > 220 and > 300, respectively) the indication criteria of biological therapy covered by the NHIF are: inefficiency of 3-month therapy with immunosuppressant (azathioprine, at a dose of 2 mg/kg unless not tolerated) and corticosteroid, or corticosteroid dependency besides immunosuppressive therapy (azathioprine at a dose of 2 mg/kg unless not tolerated), or in case of corticosteroid refractory disease, or in case of immunosuppressant contraindication. Biological therapy is covered by the NHIF in severe luminal CD when CDAI > 300 constantly during 4-week corticosteroid therapy (there is no time to start immunosuppressive therapy) [7]. In fistulizing CD with complex perianal fistula, biological therapy is covered by the NHIF when the combination of antibiotic and immunosuppressive therapy is inefficient (perianal disease activity index, PDAI > 4) or contraindicated [8].

In severe luminal paediatric CD (paediatric Crohn's disease activity index, PCDAI > 30) the indication criteria of biological therapy covered by the NHIF are: in case of corticosteroid dependency besides immunosuppressive therapy, or in case of corticosteroid refractory disease, or in case of immunosuppressant contraindication. In severe, active fistulizing paediatric CD biological therapy is covered by the NHIF when the combination of antibiotic and immunosuppressive therapy is inefficient or contraindicated [9].

In 2006 – 2010 the following biological agents were available in Hungary: *adalimumab* (available from before 2006) in RA, AS, PsA, JIA, PP, CD; *certolizumab pegol* in RA (available from 2010); *etanercept* (available from before 2006) in RA, AS, PsA, JIA, PP; *golimumab* (available from 2010) in RA, AS, PsA; *infliximab* (available from before 2006) in RA, AS, PsA, PP, CD, UC; *rituximab* in RA (available from 2007); *tocilizumab* in RA (available from 2010); *ustekinumab* in PP (available from 2010). All biological agents except rituximab are first line therapies; rituximab is a second line therapeutic option in rheumatoid arthritis.

In the case when the above mentioned requirements are not met but biological therapy is indicated, it can be obtained via another way with additional permission. The cost of biological therapy obtained in this way is covered by the NHIF by the so-called individual patient-based reimbursement.

With an exception of biological therapy in UC and CD until November 2008, biological therapy has been carried out in out-patient care and biological agents have been prescribed. Until November 2008, biological therapy in UC and CD was carried out in in-patient care and biological agents were not prescribed.

According to the contract between the NHIF and pharmaceutical companies or distributors there is a limit in the total

Table 1. Total number of patients receiving biological therapy (summing all mentioned therapeutic areas) and its cost in 2006 – 2010.

	2006	2007	2008	2009	2010
Total cost of biological therapy per year (million Euro)	6.897	13.501	23.700	40.316	55.317
Cost of biological therapy per patient per year (Euro)	7 964	8 207	8 275	9 272	9 229
Number of patients receiving biological therapy in current year	866	1 645	2 864	4 348	5 994
Number of patients receiving biological therapy in previous year(s) but not in current year	48	150	334	641	1 043

cost of biological therapies (summing all therapeutic areas) covered by the NHIF. Costs exceeding this limit are paid by the pharmaceutical companies (so-called reimbursement volume agreement).

Our aim was to give an overview of the NHIF data of biological therapy in the above mentioned inflammatory conditions.

2. Methods and materials

2.1 Data collection and registration

Hungary does not have a system of electronic prescribing, yet, but pharmacies are computerized and data related to prescribed medications are registered by these computer systems. The data warehouse of the NHIF contains the following data about prescriptions: time of prescribing, time of dispensing, patient's individual insurance code, prescribing doctor's code, prescribed medication's name and amount, International Classification of Diseases (ICD)-10 code, name and address of pharmacy, individual identification code of the prescription, and generated data such as the total price of the prescribed medication, the amount of subsidization by the NHIF, the price paid by the insured person.

The NHIF is the one and only state-owned health insurer and the one and only health insurer providing the whole spectrum of health care services. The Hungarian NHIF possesses a database (but no clinical data) related to the health care services in the past 18 – 20 years.

Some clinical data are available by the help of regular national clinical auditing. There were no register data or clinical data other than year of diagnosis (i.e., onset) of inflammatory condition, date of start of biological therapy available of the therapeutic areas described. Ethics approval was not required, and data handling of the Hungarian NHIF is strictly regulated by specific data protection acts. All legal regulations were met.

2.2 Data selection

From the data warehouse of the NHIF data of patients were selected in the period 2006 – 2010 according to the following criteria: who were dispensed specific biological agents (determined below) at least twice, whose sum subsidy was more than zero of these biological agents, and that these biological

agents were prescribed with specific ICD-10 codes. By setting the sum subsidy of biological agents more than zero we excluded cases when prescription data were not properly registered at the pharmacy and therefore were zeroed out. The specific biological agents are as follows:

Adalimumab: Anatomical Therapeutic Chemical Classification System (ATC) code L04AB04 and L04AA17, certolizumab pegol: ATC code L04AB05, etanercept: ATC code L04AB01 and L04AA11, golimumab: ATC code L04AB06, infliximab: ATC code L04AB02 and L04AA12, rituximab: ATC code L01XC02, tocilizumab: ATC code L04AC07, ustekinumab: ATC code L04AC05.

The ICD-10 codes are the following: for rheumatoid arthritis ICD: M05 and M06; for ankylosing spondylitis ICD: M45; for psoriatic arthritis ICD: M070, M071, M072, M073, L4050; for juvenile idiopathic arthritis ICD: M08; for plaque psoriasis ICD: L4003, L4004, L4005; for ulcerative colitis ICD: K518, K519; for Crohn's disease ICD: K5001, K5011, K5012, K5081, K5082. As ICD-10 codes were not obligatory content of prescriptions till the second half of 2006, data were selected without taking ICD-10 codes into consideration in 2006.

Until November 2008 biological therapy in ulcerative colitis and Crohn's disease was carried out in the in-patient care and biological agents were not prescribed, the cost of biological therapy was included in the in-patient care expenditures that are based on fixed prices of the homogenous disease group and cannot be directly calculated from it. Therefore the cost of biological therapy in ulcerative colitis and Crohn's disease till November 2008 was not included in our analysis. An important remark has to be made as the number of patients with ulcerative colitis and Crohn's disease receiving biological therapy in the in-patient care was very minimal (in the system until 2008) (data not shown). The change in the financing of these therapies in the above mentioned diseases, that is, covering the costs from the budget of medicines (prescribed medicines) resulted in a prompt increase in patient numbers.

Data from the individual patient-based reimbursement were not included in the analysis.

2.3 Costs

The costs in Hungarian Forint (HUF) were converted into Euro. In our analysis the Euro:HUF rate was calculated at

Table 2. Number of patients receiving biological therapy and its cost (million Euro) covered by the NHIF in Hungary in different therapeutic areas in 2007 – 2010.

Therapeutic area	2007		2008		2009		2010		change between 2007 and 2010 in:	
	cost (% of total)	n (% of total)	cost	n						
Juvenile idiopathic arthritis	0.603 (4.5%)	115 (7.0%)	0.713 (3.0%)	133 (4.6%)	0.848 (2.1%)	163 (3.7%)	1.053 (1.9%)	206 (3.4%)	1.75-fold ↑	1.79-fold ↑
Ulcerative colitis	0.213* (1.6%)	52* (3.2%)	0.443 (1.9%)	99 (3.5%)	1.018 (2.5%)	228 (5.2%)	1.823 (3.3%)	357 (6.0%)	Not informative*	Not informative*
Psoriatic arthritis	0.622 (4.6%)	121 (7.4%)	1.297 (5.5%)	239 (8.3%)	2.860 (7.1%)	431 (9.9%)	4.457 (8.1%)	644 (10.7%)	7.17-fold ↑	5.32-fold ↑
Crohn's disease	data n.a.*	1 (0.06%)	0.073 (0.3%)	23 (0.8%)	3.034 (7.5%)	369 (8.5%)	5.407 (9.8%)	580 (9.7%)	Data n.a.*	Data n.a.*
Plaque psoriasis	0.472 (3.5%)	67 (4.1%)	1.113 (4.7%)	154 (5.4%)	3.884 (9.6%)	428 (9.8%)	6.763 (12.2%)	682 (11.4%)	14.33-fold ↑	10.18-fold ↑
Ankylosing spondylitis	2.323 (17.2%)	318 (19.3%)	4.200 (17.7%)	540 (18.9%)	8.317 (20.6%)	843 (19.4%)	11.087 (20.0%)	1 082 (18.1%)	4.77-fold ↑	3.40-fold ↑
Rheumatoid arthritis	9.266 (68.6%)	1 188 (72.2%)	15.860 (66.9%)	1 946 (67.9%)	20.355 (50.5%)	2 450 (56.3%)	24.727 (44.7%)	3 148 (52.5%)	2.67-fold ↑	2.65-fold ↑
Total [†]	13.501	1 645	23.700	2 864	40.316	4 348	55.317	5 994	4.10-fold ↑	3.64-fold ↑

*Data not available or not informative due to therapy carried out in in-patient care.

[†]Summed number of patients exceeds the total (distinct) number of patients who received biological therapy as there were patients whose ICD-10 code changed according to prescription data (due to administrative mistake or change in clinical features).

n: Number of patients n.a.: Not available.

Table 3. Cost of biological agents (market share) covered by the NHIF in Hungary in 2006 – 2010 (million Euro) (summing all therapeutic areas).

Biological agent	2006	2007	2008	2009	2010
Adalimumab (%)	2.187 (31.7%)	4.442 (32.9%)	7.248 (30.6%)	11.635 (28.9%)	16.251 (29.4%)
Certolizumab pegol (%)	–	–	–	–	0.225 (0.4%)
Etanercept (%)	2.860 (41.5%)	4.997 (37.0%)	8.027 (33.9%)	11.519 (28.6%)	13.382 (24.2%)
Golimumab (%)	–	–	–	–	2.504 (4.5%)
Infliximab (%)	1.850 (26.8%)	3.740 (27.7%)	6.928 (29.2%)	14.935 (37.0%)	18.343 (33.2%)
Tocilizumab (%)	–	–	–	–	1.625 (2.9%)
Rituximab (%)	–	0.323 (2.4%)	1.497 (6.3%)	2.227 (5.5%)	2.524 (4.6%)
Ustekinumab (%)	–	–	–	–	0.462 (0.8%)
Σ (100%)	6.897	13.501	23.700	40.316	55.317

1:300, the rate at the time of manuscript preparation (May-June-July 2012) varied between 1:290-300.

3. Results

3.1 Total number of patients receiving biological therapy and its cost

The number of patients receiving biological therapy shows a constant increasing tendency from 866 in 2006 to 5994 in 2010, resulting in an almost 7-fold increase (Table 1). In parallel with growing patient numbers, the annual cost of biological therapy summing all therapeutic areas shows a more than 8-fold increase from approximately 6897 Euro in 2006 to more than 55317 Euro in 2010 (Table 1). A slight increase in the first three years (2006 – 2008) in the annual cost of biological therapy per patient can be observed, followed by a more prominent increase in the total annual cost from 2009 (Table 1).

Compared to number of patients receiving biological therapy in current years an increasing but still moderate number of patients receiving biological therapy in previous year(s) but not in current years was observed.

3.2 Number of patients receiving biological therapy and its cost in different therapeutic areas

Table 2 shows the number of patients receiving biological therapy and its cost in different therapeutic areas annually between 2007 and 2010. As ICD-10 codes were not obligatory content of prescriptions till the second half of 2006, data from 2006 were not included in this analysis. Until November 2008, biological therapy in UC and CD was carried out in the in-patient care and biological agents were not prescribed, the cost of biological therapy was included in the in-patient care expenditures and cannot be directly

calculated from it. Therefore results concerning UC and CD are not informative in this analysis.

Data show a constant increase in number of patients and cost of biological therapy in all therapeutic areas, albeit trends are different. When data from 2007 are compared to data from 2010, altogether there was a 3.64-fold increase in the number of patients that resulted in a 4.1-fold increase in costs (Table 2). In RA and JIA the number of patients and costs increased proportionately; 2.65-fold increase in number of patients, 2.67-fold increase in cost and 1.79-fold increase in number of patients, 1.75-fold increase in cost, respectively (Table 2). In the other therapeutic areas cost of biological therapy increased at a higher rate than the number of patients receiving that. There was a 5.32-fold increase in number of PsA patients leading to a 7.17-fold increase in costs (Table 2). In PP the 10.18-fold increase in the number of patients resulted in a 14.33-fold increase in costs, and a 3.4-fold increase in the number of AS patients led to a 4.77-fold increase in costs (Table 2). The rates of increase were the highest in PP.

3.3 Market share of biological agents

In Table 3 data from 2006 reflect the leading position of etanercept. Adalimumab, etanercept and infliximab were the biological agents available from the beginning period of our analysis (and even before 2006). As other biological agents entered the market, adalimumab and etanercept gradually lost a proportion of their market share: adalimumab to a lesser extent (from 31.7% to 29.4%), etanercept to a greater extent (from 41.5% to 24.2%) (Table 3). Nevertheless, the market share of infliximab showed a constant increase until reaching its peak in 2009 (from 26.8% to 37%), followed by a slight decrease in 2010 (33.2%) that is still higher than any other biological's that year. Rituximab, the only second line

Table 4. Comparison of annual cost of biological agents per patient in different therapeutic areas in 2007 and 2010 (Euro).

Biological agent	Infliximab		Adalimumab		Etanercept		Rituximab		Golimumab		Certolizumab		Tocilizumab		Ustekinumab	
	2007	2010	2007	2010	2007	2010	2007	2010	2007	2010	2007	2010	2007	2010	2007	2010
Rheumatoid arthritis	6 370	7 070	8 030	9 130	7 870	8 570	4 670	7 270	n.a.	6 270	n.a.	5 100	n.a.	4 670	-	-
Ankylosing spondylitis	10 000	11 500	4 900	8 730	6 530	8 300	-	-	n.a.	6 370	-	-	-	-	-	-
Psoriatic arthritis	8 430	10 500	5 430	7 730	5 930	7 800	-	-	n.a.	5 600	-	-	-	-	-	-
Juvenile idiopathic arthritis	-	-	8 300	6 100	7 270	6 370	-	-	-	-	-	-	-	-	-	-
Plaque psoriasis	9 300	11 230	n.a.	7 160	5 400	8 430	-	-	-	-	-	-	-	-	n.a.	8 570
Crohn's disease	data n.a.*	7 430	n.a.	8 570	-	-	-	-	-	-	-	-	-	-	-	-
Ulcerative colitis	data n.a.*	7 833	-	-	-	-	-	-	-	-	-	-	-	-	-	-

*Data not available due to therapy carried out in in-patient care.

n.a.: Not available.

biological agent for the treatment of RA is available in Hungary from 2007. Its market share showed first an intense later turning to a slighter increase from 2.4% to 4.6% in 2010 (Table 3). Certolizumab, tocilizumab, and golimumab entered the Hungarian market in 2010, their market share (0.4%, 2.9%, and 4.5%, respectively, Table 3) reflect that the first two biological agents are available in RA only, while golimumab is used in RA, AS, and PsA as well.

3.4 Annual cost of biological agents per capita in different therapeutic areas

Per capita annual costs of biological agents were higher in 2010 compared to 2007. The reimbursement volume agreement is operating from 2009, so data from 2010 reflect the situation under these circumstances while data from 2007, the situation before it. According to the annual per capita costs the descending order of biological agents in different therapeutic areas are as follows (Table 4):

- In RA: adalimumab > etanercept > rituximab > infliximab > golimumab > certolizumab > tocilizumab
- In AS: infliximab > adalimumab > etanercept > golimumab
- In PsA: infliximab > etanercept > adalimumab > golimumab
- In JIA: etanercept > adalimumab
- In PP: infliximab > etanercept > adalimumab
- In CD: adalimumab > infliximab

The overall rank of the costliest annual per capita costs from each therapeutic area is: 1. infliximab in AS (11500 €), 2. infliximab in PP (11230 €), 3. infliximab in PsA (10500 €), 4. adalimumab in RA (9130 €), 5. adalimumab in CD (8570 €), 6. infliximab in UC (7833 €), 7. etanercept in JIA (6370 €) (Table 4).

The price of the individual biological agents did not change over the years.

3.5 First choice of biological agent

The distribution of first choice of biological agents in different therapeutic areas is presented in Figure 1. Etanercept was the initial biologic most frequently used in patients with RA, JIA, and PP (Figure 1). Infliximab represented the largest proportion of first biological agent in AS patients and adult patients with CD (Figure 1). The most frequent choice of the first biologic was adalimumab in PsA patients (Figure 1). There were no therapeutic options available other than infliximab in UC and paediatric CD.

3.6 Time from diagnosis to start of biological therapy

Due to a national audit clinical data of patients starting biological therapy between 1st August 2009 and 31st December 2010 were available for our analysis in adults with RA, AS, PsA, PP, UC, and CD. Minimum values show that there

Table 5. Time from year of diagnosis to year of start of biological therapy among patients starting biological therapy between 1st August 2009 and 31st December 2010 (based on results from national audit).

		Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Plaque psoriasis	Ulcerative colitis	Crohn's disease
Time from year of diagnosis to year of start of biological therapy (years)	Minimum	0	0	0	0	0	0
	25% percentile	2	1	1	7	3	3
	Median	6	4	5	14	7	6
	75% percentile	12	13	12	24	13	11
	maximum	55	47	49	60	33	41
	Mean	8.5	8.6	8.8	16.3	8.9	7.9
	SD	8.4	9.7	9.9	12.0	7.0	6.6
Number of patients whose documentations were included in audit and analysis (n)		922	366	188	337	167	359

SD: Standard deviation.

Table 6. Total* annual turnover of biological agents in Denmark in 2006 – 2010 (million Euro).

	2006	2007	2008	2009	2010
Etanercept	23.809	30.054	36.184	40.862	43.062
Infliximab	24.370	27.943	35.562	41.541	45.630
Adalimumab	20.557	30.623	44.491	57.046	64.962
Certolizumab pegol	-	-	-	0.111	1.200
Golimumab	-	-	-	0.054	2.278
Ustekinumab	-	-	-	2.488	3.705
Tocilizumab	-	-	-	1.419	3.915
Σ	68.735	88.620	116.238	143.521	164.752

0 or 0.0 The value is so small that it can not be displayed after rounding.

*Total turnover: primary sector + hospital sector.

-: No sale, no data or not calculated; Euro: (Danish Krone) DKK rate was calculated at 1:7.45.

were patients receiving biological therapy in the year of diagnosis. Twenty-five percent percentile values are the lowest in AS and PsA, median values are the lowest in AS, 75% percentile values are the lowest in CD (Table 5). The lowest maximum value was observed in UC (33 years), while the lowest mean period between year of diagnosis and start of biological therapy was 7.9 years in CD (Table 5). The highest values from all aspects were detected in PP: 25% percentile was 7 years, median was 14 years, 75% percentile was 24 years, maximum was 60 years, and mean was 16.3 years (Table 5). Standard deviations were high in all therapeutic areas ranging from 6.6 years in CD to 12 years in PP.

4. Discussion

We are the first to report comprehensive data regarding biological therapy in several inflammatory conditions in Hungary. Though mostly not clinical, our data show interesting aspects of this field.

In line with the growing number of patients receiving biological therapy a constant increase in its costs can be observed. Besides the growing number of patients in all therapeutic

areas the proportion of patients changed; there was an increase in UC, CD, PsA, and PP, while a decrease in the proportion of RA and JIA patients can be observed. In AS a slight decrease is followed by a slight increase and decrease again.

According to clinical guidelines or financing protocols, there is no regulation so far that would allow tapering or discontinuation of biological therapy in psoriasis and rheumatic diseases—the largest proportion of patients with biological therapy—when patient's condition improves. Our overall data reflect the result of the lack of such regulation.

Though infliximab was the first biologic used in Europe, etanercept was the very first biological agent available in Hungary. Our data show the leading position, the highest market share of etanercept in 2006. By 2010, as other biological agents entered the market, despite the growing number of patients receiving etanercept, it lost a relatively large proportion of its market share. In parallel with this, though to a lesser extent, similar tendency of the market share of adalimumab can be observed. The reason for these tendencies is, as mentioned, the entrance of other, new biological agents, namely rituximab that gained market share by 2010, and golimumab and certolizumab that were available in 2010 the earliest.

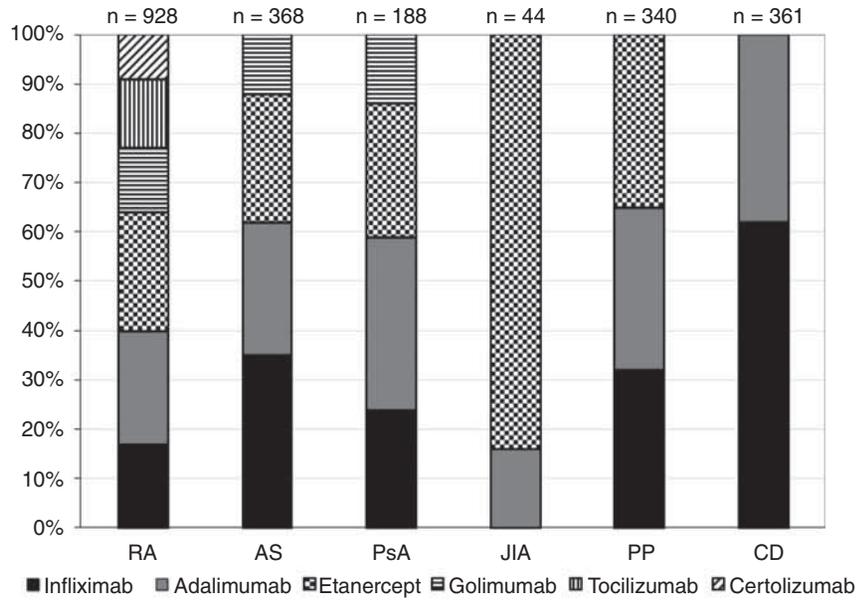


Figure 1. First choice of biological agents among patients starting biological therapy between 1st August 2009 and 31st December 2010.

AS: Ankylosing spondylitis; CD: Crohn's disease; JIA: Juvenile idiopathic arthritis; n: Number of patients; PP: Plaque psoriasis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis.

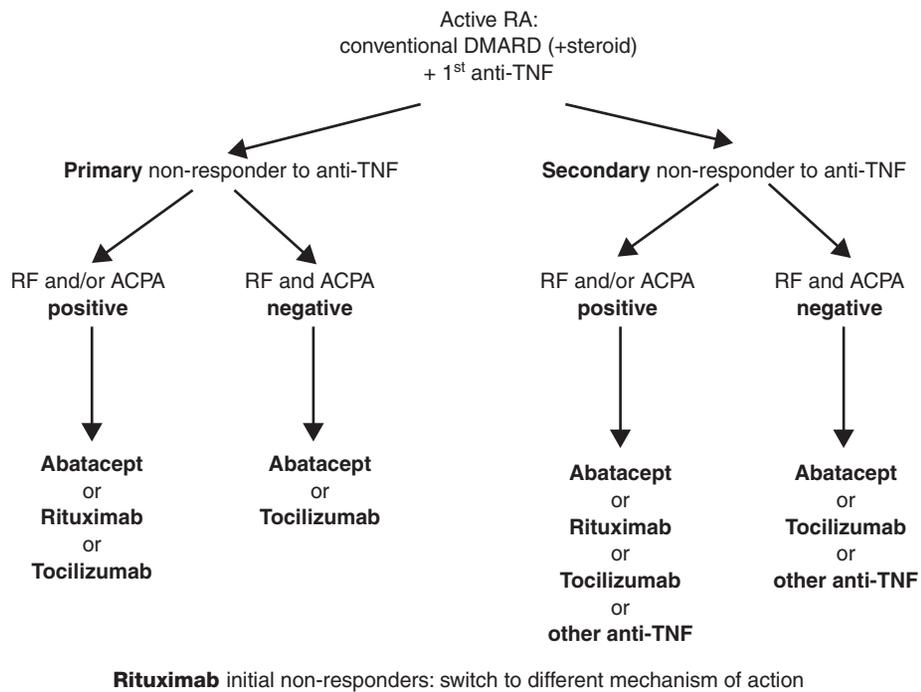


Figure 2. Treatment algorithm for patients with RA who have failed conventional treatment with DMARDs and treatment with one TNF inhibitor, as suggested by Tak [14].

Permission approved by author.

ACPA: Anti-citrullinated peptide antibody; primary non-responder: No clinical response achieved 12-16 weeks after initiation of anti-TNF treatment; RF: Rheumatoid factor; secondary non-responder: Initial clinical improvement followed by loss of response \geq 24 weeks after initiation of anti-TNF treatment.

By contrast, the other biological agent available in 2006, infliximab gained market share by 2010. This increase is the result of the increase in the number of UC and CD patients, for whom infliximab is the one and only therapeutic option as is in UC and in paediatric CD or is one of the two possibilities in adult CD.

According to a Danish online database (www.medstat.dk) significantly higher expenditures are spent on biological therapy in the Danish system (Table 6). The overall data of all therapeutic areas—not only the ones we included in our analysis—are displayed here and presumably both on and off label use was included. We did not compare data regarding rituximab as its application in cancer therapy could not be discriminated. The population of Hungary is approximately 10 million, almost twice the population of Denmark which is 5.5 million. The total Danish expenditures of biological therapy (excluding rituximab) is 9.97 times higher in 2006; 6.56, 4.9, 3.56, and 2.98 times higher in 2007, 2008, 2009, and 2010, respectively, compared to the Hungarian expenditures (where rituximab was included in the total expenditures).

Due to the reimbursement volume agreement operating from 2009 till the beginning of 2012, pharmaceutical companies or distributors paid the cost of biological therapy exceeding the agreed limit (not public information). This means that the costs covered by the NHIF are lower than the total costs displayed here.

In case of the reimbursement volume agreement there is no individual limit for each biological agent; the reimbursement is paid by the companies to the extent of the costs exceeding the limit set for the overall costs of biological therapies (i.e., one limit for the sum of costs of biological therapies) at the end of the fiscal year—together with tax and other types of reimbursement. The conditions are the same for every company; reimbursement is calculated according to the turnover, that is, market share of their products. The reimbursement volume agreement is not outcome or performance based, it does not take clinical endpoints or quality-adjusted life year (QALY) into consideration, only market share.

A constant increase in the overall annual cost of biological therapy per patient as well as the annual cost of each biological agent per patient was observed. There was a marked increase in the annual cost of biological therapy per patient in 2009 compared to previous years. This may be attributed to the operation of the reimbursement volume agreement. The expenses are affected by the relative cost of biological agents as well as the duration these agents were applied. Higher relative cost of a biological agent or longer duration of its application, or the combination of these two can be amounted to higher annual cost. As the price of biological agents did not change over the years, higher relative cost may result from increasing individual doses, certainly in the case of biological agents when increasing dose is possible. The reimbursement volume agreement could possibly provide circumstances under which increasing doses could become more frequent.

As more biological agents entered the market more therapeutic options were available in the case when another one failed. This means that biological therapy was possible to be continued with other agents and did not have to be halted due to lack of biological alternatives, resulting in higher annual cost of overall biological therapies (instead of returning to synthetic DMARDs or other therapeutic options which expenses are lower than biological therapies). To be able to distinguish the reasons more information including duration of therapy with each biological agent is required.

Adalimumab was available from only 13 years of age but etanercept was available from 4 years of age in the treatment of JIA in the period analyzed. Therefore, as reflected by our data, etanercept was used in more cases as initial biological in JIA.

Data concerning time from diagnosis to start of biological therapy show that a significant proportion of patients in the analyzed therapeutic areas received biological therapy relatively late. It is essential to start biological therapy as soon as synthetic DMARDs or other immunosuppressive medications are not effective as the longer the delay the more loss of function and disease burden is caused and the less is gained by applying expensive biological therapy.

Acute flare of UC and CD can be presented by life-threatening manifestations, rheumatic conditions can be painful, but psoriasis—at least for a longer time—may be the least disturbing condition for the patient and may bring about a visit to a medical specialist later than other previously mentioned conditions. This may partially be the reason why values related to time from diagnosis to start of biological therapy are the highest in psoriasis.

5. Expert opinion

Our review was intended to contribute to future decisions in order to maintain a sustainable system of anti-inflammatory biological therapies while enforcing clinical aspects. It has already been stated that unrestricted use of biologic therapies would not be affordable, according to a British data [10].

Anti-inflammatory biological therapy is essential to combat loss of function and prevent complications due to chronic inflammation when other therapeutic options like synthetic DMARDs and “conventional” immunosuppression fail. Therefore it is crucial that biological agents are applied as early as possible when inflammation control requires it. Losing time in commencing biological therapy may lead to irreversible loss despite the costly therapeutic options (biological agents). Nevertheless, from the point of view of outcomes, the cost per QALY for biological therapy with additional MTX in newly diagnosed RA patients (so-called early arthritis) was far beyond the limit that is acceptable by most health care systems, indicating that the treatment was not cost-effective in this group of patients [11]. Due to the high costs and severe possible side effects, biological therapies should be applied according to stringent regimen. According to a

systematic review of cost-effectiveness, alternative treatment (non-biological DMARDs) has been confirmed to be the early, initial treatment in RA, and biological therapy is only cost-effective after the failure of synthetic DMARDs [12].

Despite the fact that biological therapy has been available in Hungary for several years, there is a significant proportion of patients who receive this type of treatment relatively late (as opposed to the possibility of early biological therapy provided by clinical and financial regulations). In general, health authorities in close collaboration with clinical decision-makers can achieve a reduction in such a delay by adjusting the care of patients, can contribute to ensuring that early detection of the disease and early initiation of proper therapies—including biological therapies—are carried out in the health care systems.

Figure 2 shows an algorithm suggested by P. P. Tak for the treatment of RA when patients fail to respond to anti-tumor necrosis factor (TNF) therapy [13]. The algorithm, by differentiating between seropositive and seronegative patients, primary and secondary non-responders, is an initiative towards personalized, tailored therapy [13]. This approach can help us to avoid less or non-effective therapies and let us apply the ones proven effective in a subgroup of patients determined by certain biomarkers, resulting in health benefits

and a decrease in expenditures. Hopefully the extensive research on biomarkers will enable the most cost-effective application of biological therapies.

Prolonging disease control by the appropriate use of non-biologic treatments may result in benefits both to patients and purchasing health authorities by delaying the need for biologic treatments, thereby providing appropriate allocation of limited health care resources [14]. Strictly along clinical guidelines the most cost-effective treatment of inflammatory conditions is the goal of all health care providers. Our aim was to contribute to information exchange between different systems.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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