Anti-Tumor Necrosis Factor Therapy: 6 Year Experience of a Single Center in Northern Israel and Possible Impact of Health Policy on Results

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Abstract

Background: Infliximab and etanercept have been included in the Israeli national list of health services since 2002 for rheumatoid arthritis and juvenile idiopathic arthritis, and since 2005 for psoriatic arthritis and ankylosing spondylitis. The regulator (Ministry of Health and health funds) mandates using fixed doses of infliximab as the first drug of choice and prohibits increased dosage. For other indications (e.g., vasculitis), anti-tumor necrosis factor therapy is given on a "compassionate" basis in severe refractory disease.

Objectives: To describe our experience with anti-TNF therapy in a single tertiary referral center in northern Israel and to analyze the impact of the national health policy on the results.

Methods: We reviewed the medical records of patients who received anti-TNF therapy in our institution, and analyzed demographic data, diagnosis, clinical and laboratory features, previous and current therapies, and anti-TNF treatment duration and side effects.

Results: Between 2001 and 2006, 200 patients received anti-TNF therapy for rheumatoid arthritis (n=108), juvenile idiopathic arthritis (n=11), psoriatic arthritis (n=37), ankylosing spondylitis (n=29), adult Still's disease (n=4), overlap disease (RA and scleroderma or polymyositis, n=6), temporal arteritis (n=1), polyarteritis nodosa (n=1), dermatomyositis (n=1), amyloidosis secondary to RA (n=1) and Wegener's granulomatosis (n=1). Forty percent of RA patients discontinued the first anti-TNF agent due to side effects or insufficient response. Higher sedimentation rate and lower or negative rheumatoid factor predicted better response to therapy among RA patients. AS and PS patients had a better safety and efficacy profile. Severe infections occurred in 2% of patients. All eight patients who presented lung involvement as part of their primary rheumatic disease remained stable or improved. A significant improvement was achieved in all six patients with overlap disease.

Conclusion: Our daily practice data are generally in agreement with worldwide experience. The 'deviations' might be explained by the local health policy at that time. The impact of health policy and economic and administrative constraints should be taken into account when analyzing cohort daily practice data.

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The treatment of inflammatory joint diseases has changed dramatically over the past few years with the introduction of anti-tumor necrosis factor agents. Anti-TNFα therapy is highly efficient; it leads to a substantial functional improvement in the great majority of patients, down-regulates inflammatory cytokines stimulated by TNFα, and delays radiological changes [1-3]. Currently available agents are infliximab (Remicade®, Centocor), etanercept (Enbrel®, Wyeth) and adalimumab (Humira®, Abbott). Infliximab and etarnecept have been included in the Israeli national list of health services ("the health basket") since 2002 for rheumatoid arthritis and juvenile idiopathic arthritis patients who failed treatment with three disease-modifying anti-rheumatic drugs. More recently (2005), they were also approved for psoriatic arthritis and ankylosing spondylitis. Adalimumab has not been included in the basket of health care in Israel, although it has been approved by the Ministry of Health for all the above indications. The present report describes our experience with anti-TNF therapy in patients with inflammatory joint diseases in a single center in northern Israel, and discusses the possible impact of our national health policy on the results.

Patients and Methods

We reviewed the medical records of all patients treated with anti-TNF agents in the Department of Rheumatology at Rambam Health Care Campus during the years 2001–2006. A small group of patients had been on anti-TNF therapy before the drug was included in the "health basket." The study was approved by the local ethics committee. Data on age; gender; diagnosis; clinical, radiological and laboratory features (disease duration, extra-articular manifestations, tender and swollen joint counts, visual analog scale of physician's global assessment of disease activity, erythrocyte sedimentation rate, hemoglobin before and after anti-TNF therapy, rheumatoid factor, antinuclear antibodies, any evidence of erosions on hands and feet X-ray films); previous and current DMARDs; response; anti-TNF treatment duration and side effects were entered into a database and analyzed. Efficacy was assessed using the Disease Activity Score (DAS28) for RA and JIA patients; tender and swollen joint count and global and pain response measures for PSA; the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS; and acute-phase reactants for all patients. Baseline and 6 month evaluations were recorded.

According to the manufacturers' recommendations, infliximab was administered intravenously at a dose of 3 mg/kg for RA and

TNF = tumor necrosis factor
RA = rheumatoid arthritis
AS = ankylosing spondylitis
PS = psoriatic arthritis
DMARDs = disease-modifying anti-rheumatic drugs

JIA, and at 5 mg/kg for AS and PSA, at the start of treatment, weeks 2 and 6, and every eighth week thereafter. Etanercept was given subcutaneously 25 mg twice weekly, and adalimumab 40 mg was administered subcutaneously every 2 weeks. For other indications (vasculitis, dermatomyositis) infliximab was given at a dose of 5 mg/kg. All patients were tested for tuberculosis and hepatitis B and C at baseline. Patients with a positive purified protein derivative test (≥ 10 mm) or findings on chest X-rays compatible with old TB received prophylactic treatment with isoniazid or rifampin. Lamivudine was administered as a prophylactic to all hepatitis B carriers treated with anti-TNF.

Statistical analysis was performed with the *t*-test and Mann-Whitney rank sum to compare the characteristics of the responder and non-responder groups. Spearman and Pearson correlation and multivariate ordinal logistic regression were used to assess the effect of baseline characteristics on response to therapy.

Results

Two hundred patients received anti-TNFα therapy in our institution. The indications for anti-TNF therapy included RA, PSA, AS, JIA, overlap disease (RA with another collagen disease), adult Still's disease, and refractory temporal arteritis, Wegener's granulomatosis, dermatomyositis, polyarteritis nodosa and amyloidosis secondary to RA, after failure of conventional therapy. Table 1 shows the demographic and clinical characteristics of the patients, their diagnoses, the duration of disease, and the number of DMARDs previously given.

Efficacy

A total of 176 patients received infliximab, 49 patients received etanercept (in 22 patients it was the first anti-TNF agent and in 27 patients the second), and two patients received adalimumab (after failure of two anti-TNF agents). Sixty-two patients (31%), mostly RA patients, discontinued therapy due to adverse events or inefficacy. Most of these patients reacted well to a second anti-TNF agent [Table 2]. In seven patients two anti-TNF agents were not effective. Altogether, 74 patients received therapy with the first anti-TNF agent for more than 18 months, and 33 of them continued it for more than 36 months. Most of the patients (83%) continued concomitant DMARDs (methotrexate in 151 patients, azathioprine in 12, leflunomide in 3), and 27.5% (55 patients) continued prednisone.

As anti-TNFα therapy was the first to be approved in the Israeli health basket for RA, the largest group comprises RA patients. Forty percent of RA patients discontinued the first anti-TNF agent due to adverse events or inefficacy. Of the 31 patients who discontinued therapy due to inefficacy 20 did so in the first 12 months (most after the first 6 months). Among the patients who received more than 18 months of therapy only one ceased taking it due to relapse (he actually stopped taking the DMARD). Thirteen RA patients discontinued the first anti-TNF due to adverse events, mostly allergic. Most of the adverse events occurred during the first year of therapy.

The differences between the responding RA patients and the non-responders (patients who interrupted therapy due to inefficacy or adverse events during the follow-up period) were analyzed. A positive significant correlation was found between disease duration, ESR and number of DMARDs ($P = 0.0023$; correlation coefficient 0.232, $P = 0.01$, correlation coefficient 0.237, respectively). A higher sedimentation rate and negative or lower titer of rheumatoid factor predicted a better response to therapy ($P = 0.04$, correlation coefficient 0.203, $P = 0.03$, correlation coefficient -0.215, respectively). No significant differences were found between the RA responders and RA non-responders in

Table 1. Demographic and clinical characteristics of patients

Diagnosis	No. of patients (females, Jews)	Mean age (yrs, range)	Disease duration (yrs, range)	Mean no. of DMARDs (range)	Mean disease activity (range)
Rheumatoid arthritis	108 (74, 69)	51.4 (21–80)	10.75 (1–35)	3.9 (1–9)	DAS 28, 7.6 (6.3–8.5)
Juvenile idiopathic arthritis	11 (7, 6)	30.3 (18–47)	21.4 (2–40)	4.33 (3–6)	DAS 28, 7.49 (6.8–8.2)
Psoriatic arthritis	37 (22, 30)	47.8 (27–68)	10.6 (2–35)	3.2 (2–7)	Swollen joints17.6 (6–28)
Ankylosing spondylitis	29 (4, 22)	45.9 (27–81)	15.1 (4–40)	1.92 (0–7)*	BASDAI 7.8 (6–9.8)
Adult Still's disease	4 (1, 2)	42.3 (34–50)	4.5 (1–12)	3	DAS 28, 7.6 (7.3–8.4)
Overlap	6 (6, 4)	54 (38–69)	8.5 (1–27)	3.83 (3–5)	DAS 28, 8.2 (7.6–8.5)
Other	5 (2, 0)	70.6 (59–78)	1.2 (0.5–2)	1.7 (1–2)	

Overlap = 5 patients with RA and scleroderma, 1 patient with RA and polymyositis
Other = 1 patient each with temporal arteritis, RA and amyloidosis, Wegener's granulomatosis, polyarteritis nodosa, dermatomyositis
* Several AS patients had severe refractory arthritis of large joints and required therapy with multiple DMARDs.

Table 2. Mean and range duration of first and second anti-TNF therapy and discontinuation rates

Diagnosis (no. of pts)	Mean duration of first anti-TNF treatment (mos) (range)	Discontinued due to adverse events (no. of patients)	Discontinued due to inefficacy (no. of patients)	Second anti-TNF (no. of patients treated/failed)	Mean duration of second anti-TNF treatment (months) (range)
RA (108)	21.1 (1–73)	13 (12%)	31 (28.7%)	*18/5	20.1 (1–72)
JIA (11)	20.4 (3–54)	2 (20%)	1 (10%)	1/1	18
PSA (37)	17.8 (1–57)	2 (5.4%)	3 (8.1%)	5/0	15.3 (10–24)
AS (29)	18.1 (1–72)	2 (7.4%)	2 (7.4%)	4/1	6 (2–10)
Adult Still's (4)	20.7 (7–30)	0	2 (50%)	2/0	6
Overlap (6)	16.5 (5–29)	2 (33.3%)	1 (16.6%)	2/0	36
Other (5)	4	0	1 (33.3%)	0	0

* The relatively small number of RA patients treated with a second anti-TNF agent is due to our participation in clinical trials aimed at this population.

TB = tuberculosis
ESR = erythrocyte sedimentation rate

Table 3. Demographic and clinical characteristics of rheumatoid arthritis patients – responders and non-responders (discontinued first anti-TNF due to adverse events)

	Continued treatment	Discontinued treatment	Statistical significance
No. of patients	64	31	
Mean duration of first anti-TNF Rx (range)	31 mos (1–73)	10.3 mos (2–26)	
Jews	67.2%	63.8%	NS
Females	62.5%	69.5%	NS
Age	54.9	50.3	NS
Disease duration (yrs)	11.8	8.3	NS
Erosive disease	75%	80%	NS
DAS 28 at baseline	7.58	7.62	NS
DAS 28 at 6 months	3.48	6.84	P < 0.01
RF positive	54.7%	72.5%	P = 0.03
ESR at baseline	54.7	45.2	P = 0.042
ESR at 6 months	20.2	41.8	P < 0.01

RF = rheumatoid factor, ESR = erythrocyte sedimentation rate

Table 4. Severe adverse events which required hospitalization and/or treatment interruption or discontinuation

Type of reaction	No. of patients
Infusion related: chest pain, chills, shortness of breath	7
Rash	6
Headache – severe	1
Severe hypertension	1
Angioedema	1
Vomiting, fever	2
Severe liver function elevation (> 5 times)	1
Septic arthritis	1
Severe respiratory infection	3
Psoriasis	1
Peripheral neuropathy	1
Subarachnoid hemorrhage	2
Lymphoma	1
Solid tumors	3

other parameters [Table 3]. Statistical analysis was performed separately for all non-responders (failed due to inefficacy or side effects) and for those who failed due to inefficacy only, and the results were similar. In PSA and AS patients, the rate of therapy discontinuation was much lower (13.5% and 13.4%, respectively) [Table 2].

Four hepatitis B carrier patients received anti-TNF therapy (infliximab and etanercept) with concomitant prophylactic lamivudine, without any hepatic worsening. Twenty patients with positive PPD tests received prophylactic anti-tuberculosis treatment with isoniazide or rifampin. No case of TB reactivation has occurred so far. Twenty patients had positive antinuclear antibodies at baseline. None developed drug-induced lupus. No patient with rheumatoid lung disease (eight patients) revealed any deterioration of lung function on serial lung function tests and chest X-rays, and two patients actually improved. No heart failure was observed. Nine patients were 70 years old or older and they tolerated the therapy without any particular problems.

Adverse events

Serious adverse events, mostly allergic reactions, occurred in 27 patients (13.5%) and led to discontinuation in 22 [Table 4].

- I*nfusion-related*: Most of the infusion-related reactions (with infliximab) were mild and resolved with a decreased rate of infusion and antihistamine therapy (given afterwards prophylactically). Ten patients had to discontinue infliximab due to severe infusion-related reactions in spite of prophylactic treatment.
- A*llergic reactions*: One patient developed severe allergic reaction to two anti-TNF agents (2 years of infliximab treatment and 2 months after etanercept administration). Another patient developed angioedema after 10 months of infliximab therapy. Severe rash led to therapy discontinuation in another six patients.
- O*ther diseases*: A patient with AS treated with infliximab developed psoriasis. The drug was stopped and he was switched to etanercept without further side effects. Peripheral neuropathy occurred in an RA patient after 2 months of etanercept therapy. Symptoms resolved following drug interruption.
- S*evere infections*: One patient suffered severe pneumonia and developed septic shock but recovered.

  Two other patients were hospitalized due to severe upper respiratory tract infection. Etanercept was temporarily interrupted in all three cases. Septic arthritis of the shoulder with *Staphylococcus aureus* developed in a psoriatic patient treated with infliximab, methotrexate and corticosteroids. Infliximab was temporarily discontinued and renewed after antibiotic therapy, without further events.
- M*alignancy*: Four patients had a malignant disorder. A 60 year old man with severe RA treated with etanercept, azathioprine and corticosteroids was diagnosed with small intestine B cell, low grade, non-Hodgkin's lymphoma after 10 months of etanercept therapy. The patient received rituximab and chemotherapy, with good response. A 50 year old man with severe adult Still's disease received methotrexate, prednisone and infliximab for 7 months and subsequently switched to etanercept for another 11 months. The anti-TNF agent was discontinued after a diagnosis of neoplastic bladder polyp. A 72 year old woman with long-standing severe RA treated with azathioprine, corticosteroids and six infusions of infliximab was evaluated following intestinal obstruction. Carcinoma of

PPD = purified protein derivative

the rectum was detected. The event was judged as probably not related to infliximab. Carcinoma of the cervix was found in a 42 year old woman with RA treated with methotrexate, hydroxychloroquine and corticosteroids, after a second infusion of infliximab. The patient was symptomatic before anti-TNF therapy and the diagnostic procedure started before initiation of therapy. The event was considered not related to the anti-TNF agent.

- *Other severe adverse events*: One patient discontinued infliximab due to fivefold elevation of liver transaminases. Concomitant methotrexate treatment was discontinued previously without any change in liver study results. When liver function levels normalized, etanercept was started without further side effects. Two patients suffered a subarachnoid hemorrhage. A small arteriovenous malformation was detected in one. Both patients recovered and anti-TNF therapy was resumed.

Discussion

Our study describes the experience of a single rheumatology center with anti-TNF therapy in rheumatic diseases. To our knowledge, this is the largest single center cohort of anti-TNF-treated patients published in Israel.

By law the entire Israeli population is insured by four major health funds. However, none of them agreed to reimburse therapies not specifically included in the "basket of health care" and our results therefore reflect the impact of administrative decisions by the Ministry of Health. Although safety data were found to be similar to worldwide experience, a few facts are worth noting: a) the high proportion of anti-TNF-treated RA patients versus PSA and AS, b) more infliximab than etanercept-treated patients; c) only minimal experience with adalimumab can be reported at the present time; d) a higher rate of therapy interruption; and e) the relatively small number of RA patients treated with a second anti-TNF agent.

Our results reflect the treatment regimens authorized by the Ministry of Health: anti-TNF therapy is approved for active RA, for JIA after failure of three DMARDS, for active PSA after failure of two DMARDs (one of them methotrexate), and for AS with axial disease after failure of non-steroidal anti-inflammatory drugs and/or salazopyrine. The maximal post-induction dose of infliximab permitted for RA and JIA is 3 mg/kg every 8 weeks, and 5 mg/kg every 8 weeks for PSA and AS. Administrative criteria are strict and dose adjustment might be problematic. Infliximab was approved as a first choice anti-TNF agent in RA (because of the temporary shortage of etanercept) in 2002. Until recently, etanercept was allowed only for patients who had failed infliximab (inefficacy or side effects). This explains the greater proportion of infliximab-treated patients. Anti-TNF therapy was included in the health basket for PSA and AS only in mid-2005, making the number of these patients smaller and the follow-up shorter. Adalimumab was approved for RA, PSA, and AS by the Israeli health ministry, but it has not yet been included in the health basket. It is almost impossible to receive anti-TNF therapy for other autoimmune diseases, but it is given in rare cases on a "compassionate" basis for severe refractory disease (as in our patients in the "others" group). Most patients cannot afford to buy the drugs on the free market because of their exhorbitant cost.

Our results indicate a higher rate of interruption of TNF blockers in daily practice, especially in RA patients, compared with clinical trials and other cohort studies [4-8]. We cannot help but wonder whether a more flexible health policy, which would have allowed adjustment of infliximab doses in partially responsive patients, might have improved the retention rates of anti-TNF agents in our patients. Most of our patients who discontinued therapy did so in the first 18 months of treatment. The rate of late therapy withdrawal was very low. Most of our patients who failed the first anti-TNF agent (inefficacy or side effects) reacted well to the second anti-TNF [Table 2]. Compared to the published literature, in our study a relatively small number of RA patients were treated with a second anti-TNF, mainly because they chose therapy with other biological agents that became available in clinical studies. In RA patients a higher sedimentation rate and lower or negative rheumatoid factor level predicted a better response. This raises the question of whether patients with high levels of rheumatoid factor need higher doses. On the other hand, our 'discontinuation rate' was lower than that reported by Douclos et al. [9]. A possible explanation might be the high proportion of concomitant DMARDs and anti-TNF therapy in our patients. Our policy is to continue DMARDs, especially methotrexate, in most patients who take anti-TNF agents, regardless of clinical improvement.

The rate of severe infections was similar to the worldwide experience – 2% [10,11] and lower than that recently reported by Salliot et al. [12]. As of the day of writing, no opportunistic infections were reported among our patients. Although rare, opportunistic infections with intracellular organisms, e.g., Listeria, have been noted in post-marketing data and several case reports [13,14].

Anti-TNF therapy was found to be safe and efficient in a small group of RA patients with coexistent collagen disease (scleroderma or polymyositis). One patient received infliximab for severe amyloidosis secondary to RA; a partial response was achieved but the patient expired. We used anti-TNF therapy on a compassionate basis for several diseases not included in the Israeli health basket as indications for anti-TNF therapy, hence our experience is limited. A patient with refractory temporal arteritis achieved a partial response. Two other patients, one with refractory Wegener's granulomatosis and one with periarteritis nodosa, reacted well to infliximab therapy. Remission was achieved in an etanercept-treated patient with refractory dermatomyositis. Malignancy was diagnosed in four patients. We cannot link any of the three cases of solid tumors to anti-TNF therapy. For solid tumors, data with etanercept and infliximab showed that the number of tumors observed during follow-up of patients treated in clinical trials was comparable to that in the general population [10,11,15]. The issue of lymphoma, however, is much more complex. A patient with severe RA treated with etanercept, azathioprine and corticosteroids was diagnosed with small intestine B cell, low grade, non-Hodgkin lymphoma after 10 months of

etanercept therapy. Patients with chronic inflammatory rheumatic diseases, such as RA, are at higher risk of developing B cell non-Hodgkin's lymphoma than the general population [16,17]. The risk has been shown to correlate with activity and severity of disease, as well as exposure to immunosuppressive agents. The current data suggest a higher rate of lymphomas in patients receiving TNF antagonists relative to the healthy population [11]. Whether the risk of lymphoma is higher with TNF antagonists than in patients receiving conventional DMARDs remains unclear; in fact, in a recently published longitudinal study of a large cohort of RA patients there was no evidence of an increased incidence of lymphoma among patients who received anti-TNF therapy [18]. The safety and efficacy profile seems to be much better in PSA or AS. This observation is in agreement with the experience of other centers [9,19].

In conclusion, our daily practice data are generally in agreement with the worldwide experience. The 'deviations' might be explained by the local health policy at that time. The impact of health policy and economic and administrative constraints should be taken into consideration when analyzing cohort daily practice data.

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