The use of TNF Blockers in the Rheumatology Outpatient Clinic, Doha, Qatar.

* Al Emadi S., **Sarakbi H., ***Hammodeh M.
Rheumatology Section, Medicine Department, Hamad Medical Corporation

Abstract:
Background: The currently available TNF blocking agents include ifliximab, etanercept and adalimumab. They are approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis in the United States and Europe. Also TNF blockers are used currently in other rheumatic and non-rheumatic disease.

Objective:
Primary objective: To evaluate our practice of using TNF blockers in the outpatient rheumatology clinics at Hamad Medical Corporation in Qatar, to evaluate the response rate to TNF blockers, and the rate of switching from one TNF blockers to another.

Secondary objective: to assess rate of serious infection and TB.

Methods: The study involved a retrospective chart review of 82 patients in rheumatology outpatient clinic since the introduction of TNF-Blockers at Hamad Medical Corporation in 2002 till December of 2005.

Results: Twenty two patients out of 82 received Infliximab (26.8%), 51 patients received etanercept (62.1%) and 22 patients received adalimumab (26.8%) including switchers and non switchers. Response rate was 82% to initial TNF blocker in RA, and almost 100% in Psoriatic arthritis and ankylosing spondylitis. Reason of switching was either due to no response or side effects. No significant serious adverse events in our cohort and no TB reactivation.

Conclusion: Our data are comparable with the international guidelines; regarding the use of TNF blockers in rheumatic disease. Also they reflect the daily practice in the rheumatology outpatient clinic in Qatar.

Keywords: Anti-TNF, TNF blocking agents., rheumatoid arthritis RA, psoriatic arthritis PSA, ankylosing Spondylitis AS, DMARDs disease modifying anti-rheumatic drugs.

Patients and Methods:
The files were reviewed retrospectively of 82 patients attending the rheumatology outpatient clinic, Hamad Medical Corporation, Qatar, between April 2002 (when TNF blockers were introduced) and December 2005. The following information was collected:
- The date of starting TNF treatment
- The diagnosis for which it was used
- DMARDs use before initiating TNF blocker.
- Demographics of each patient, age, sex, past DMARDs use, and results of PPD skin tests and chest x-ray.
- Serious side effects:
- Switching to another TNF blocker and the reason for switching (lack of response, loss of response, side effect).

During the period April 2002 and December 2005 patients were treated with etanercept by subcutaneous injection of 25 mg twice weekly or 50 mg once/week, adalimumab was administered as a subcutaneous injection of 40 mg every two weeks and Infliximab as an infusion at 0, 2, 6, and 8 weeks and every 8 weeks thereafter. Infliximab was administered in combination with methotrexate for RA patients.

Results:
A total of 82 patients’ files were reviewed. There were:
- 46 cases of rheumatoid arthritis (RA) (56%).
- 20 cases with psoriatic arthritis (24%).
- 8 cases with ankylosing spondylitis (AS) (17%) and one case in each of reactive arthritis, Behcet’s disease, relapsing polychondritis and prolapsed disc (2.1%).

Rheumatoid arthritis patients (RA):
Five males and 41 females had all failed at least one DMARD. All had received and had failed to respond to treatment with methotrexate (MTX); 12 patients (26%) had received MTX and Leflunamide. All the patients had a PPD skin test and chest x-ray before starting TNF blockers; only one had a positive PPD skin and was started on (INH) isoniazide 300 mg /
The use of TNF Blockers in the Rheumatology . . .

Al - Emadi S., et al.

day for six months and was followed in the TB clinic. Table 1 shows the demographic data of patients with RA.

Table 1-

<table>
<thead>
<tr>
<th>Age</th>
<th>16-60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>41 females , 5 males</td>
</tr>
<tr>
<td>Nationality</td>
<td>11 non Qatari’s /35 Qatari’s</td>
</tr>
<tr>
<td>DMARDs</td>
<td>Methotrexate 46 pts</td>
</tr>
<tr>
<td></td>
<td>Azathioprine 4 pts</td>
</tr>
<tr>
<td></td>
<td>Prednisone 23 pts</td>
</tr>
<tr>
<td></td>
<td>Hydroxychloroquine 8 pts</td>
</tr>
<tr>
<td></td>
<td>Leflunamide 12 pts</td>
</tr>
<tr>
<td></td>
<td>NSAID 46 pts</td>
</tr>
</tbody>
</table>

TNF blockers use in RA:

As an initial Anti-TNF agent; six patients received Infliximab (13%), 30 patients received etanercept (65%) and 17 patients received adalimumab (37%).

Seven of the 30 patients who received initially etanercept (23%) was switched from etanercept to adalimumab;
- Three due to lack or loss of response
- Four due to side effects: one due to rash and hair loss, two due to injection site irritation, and another due to hair loss.

One patient was switched from Infliximab to etanercept due to lack of a response.

One patient on etanercept was lost to follow up as she left Qatar.

Table 2

<table>
<thead>
<tr>
<th>TNF Blockers</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6/46</td>
<td>30/46</td>
<td>17/46</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>65%</td>
<td>37%</td>
</tr>
</tbody>
</table>

Results for psoriatic arthritis (PSA)

Eight males and 12 females had psoriatic arthritis; most had failed more than two DMARDs. All had negative PPD skin tests and chest x-ray.

Table 3

<table>
<thead>
<tr>
<th>Age</th>
<th>49 +/- 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>All males</td>
</tr>
<tr>
<td>Nationality</td>
<td>5 non Qatari /3 Qatari</td>
</tr>
<tr>
<td>No. of NSAID</td>
<td>More than 2 in all</td>
</tr>
<tr>
<td>Previous DMARDS</td>
<td>Methotrexate in 3</td>
</tr>
<tr>
<td></td>
<td>Sulphasalazine in 6</td>
</tr>
<tr>
<td></td>
<td>Pamidronate in 1</td>
</tr>
</tbody>
</table>

TNF blockers in PSA:

Eight of 20 patients (40%) received Infliximab, 17 patients (85%) received etanercept and two patients received adalimumab (10%).

Six of 20 patients (30%) were switched from one anti-TNF agent to another for the following reasons:

One patient was switched from etanercept to adalimumab due to a lack of response; one patient switched from etanercept to Infliximab due to dizziness and lack of response. This patient was also switched from Infliximab to adalimumab again showed no response then started on ALEFACEPT 15 mg intramuscular and had a good response.

One patient was switched from Infliximab to etanercept due to no response; The fourth patient was switched from etanercept to Infliximab because of non response, the fifth patient was switched from Infliximab to etanercept due to lung infection and the sixth patient was switched from Etanercept to adalimumab due to non response.

Table 4 . The use of TNF blockers in PSA

<table>
<thead>
<tr>
<th>TNF Blockers</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8/20 (40%)</td>
<td>17/20 (85%)</td>
<td>2/20 (10%)</td>
</tr>
</tbody>
</table>

Results for ankylosing spondylitis:

Eight AS patients, all males, had failed to respond to two or more NSAIDs for at least three months each and had failed one or two DMARDS.

Table 5 . AS patients characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>12 females/8 males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>15 Qatari’s /5 non Qatari’s</td>
</tr>
<tr>
<td>Nationality</td>
<td>Methotrexate 15 patients</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine 2 patient</td>
</tr>
<tr>
<td></td>
<td>Prednisone 4 patients</td>
</tr>
<tr>
<td></td>
<td>Leflunamide 3 pts</td>
</tr>
<tr>
<td></td>
<td>Azathioprine 1 pt</td>
</tr>
<tr>
<td></td>
<td>Sulphasalazine 4 pts</td>
</tr>
<tr>
<td>NSAID</td>
<td>20 pts</td>
</tr>
</tbody>
</table>

TNF blockers in AS

Five patients received Infliximab (62.5%), three patients received etanercept (37.5%) and two patients received adalimumab (25%).

Two patients out of 8 (25%) switched their TNF blockers, the first patient switched from etanercept to adalimumab due to recurrent boils infection with the former and the second patient was switched from Infliximab to etanercept because of non- response.

Table 6 TNF in AS

<table>
<thead>
<tr>
<th>TNF Blockers</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5/8 (62.5%)</td>
<td>3/8 (37.5%)</td>
<td>2/8 (25%)</td>
</tr>
</tbody>
</table>
The use of TNF Blockers in the Rheumatology

Al - Emadi S., et al.

Other conditions for which TNF blockers were used:

One patient (2.1%) with reactive arthritis in the form of tendenopathies failed to respond to methotrexate and Leflunomide and was successfully treated with adalimumab with no relapse.

One patient with Behcet’s disease who had uveitis was treated with Infliximab with good response.

One patient with relapsing polychondritis received Infliximab, but developed shortness of breath during infusion then was switched to etanercept and showed partial response.

One patient received one infusion of infliximab for severe prolapsed disc that showed a good response.

All cohort TNF

Table 7

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/82 (27%)</td>
<td>51/82 (62%)</td>
<td>22/82 (27%)</td>
</tr>
</tbody>
</table>

Response rate to TNF blockers in all:

Out of the 82 cases, the response rate was as follows:

In RA there was 36/46 patients (82%) with no active disease with TNF blockers in the non switchers and the switchers then had a good response rate too. In PSA all had a good response also in AS.

Adverse events in 82 patients: there were no significant serious adverse events in our cohort, as only one patient who developed salmonella septic arthritis, required intravenous antibiotics and admission to the hospital, during which time etanercept was stopped and resumed afterwards with no further complications. Another patient developed recurrent nostril infections requiring oral antibiotics and was switched from etanercept to adalimumab and one patient developed pneumonia.

Other side effects were not serious, being local site irritation, hair loss, weight gain, and dizziness.

Out of the 82 patient only one had a positive skin test with normal chest-x-ray and required prophylaxis with INH before starting TNF-blockers but there was no reactivation of TB.

Table 8 adverse events

<table>
<thead>
<tr>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 salmonella septic arthritis</td>
<td>1 lung infection</td>
<td>4 injection site irritation</td>
</tr>
<tr>
<td>2 hair fall</td>
<td>1 chest tightness</td>
<td></td>
</tr>
<tr>
<td>1 nostril infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 severe boil infection of the skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 injection site irritation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion:

The currently available anti-TNF agents infliximab, etanercept, and adalimumab are approved for the treatment of rheumatoid arthritis (RA) ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PsA) in the USA and Europe. Infliximab, etanercept and adalimumab are all potent neutralizers of bioactivity of TNF alpha, a key cytokine of importance in the pathogenesis of RA, AS, and PsA but there are fundamental differences between the three agents that might explain a differential effect.

Infliximab is a chimeric monoclonal antibody with a murine variable and a human IgG1. Adalimumab is a fully humanized monoclonal antibody. Etanercept is a genetic fusion of recombinant soluble p75 TNF alpha receptor and the Fc portion of human IgG (IgG1).

Although all three bind to TNF alpha, etanercept also binds to lymphotoxins and has been found in rheumatoid synovial tissue. Although its role remains to be defined, recent work has also shown that complexes formed between etanercept and both soluble and transmembrane TNF alpha are less stable than those formed with Infliximab. Both Infliximab and etanercept have been shown to induce apoptosis of macrophages but not lymphocytes in rheumatoid synovia. However only Infliximab has been shown to induce apoptosis in lamina propria T-lymphocytes in patients with Chron’s disease, which could be one possible explanation for the differential efficacy of Infliximab and etanercept in Chron’s disease.

There are also differences in the half lives of the three agents, with etanercept having the shortest half-life, only four days and adalimumab having the longest 14 days. The three drugs also differ in their dosing regimens; Infliximab is given as an infusion at 0,2,4,6, then every eight weeks starting with a dose of 3 mg/kg in RA and 5 mg/kg in PSA, whereas etanercept is given as 25 mg twice/week or 50 mg /week, and adalimumab is administered as 40 mg subcutaneously every two weeks.

Finally, anti-TNF alpha agents are associated with the development of antibodies directed against the drug. The rate may be higher in patients receiving Infliximab due to its chimeric component. The effects of these antibodies are not clear but may be associated with drug reactions and loss of efficacy over time. Studies of adalimumab and Infliximab have shown that the addition of methotrexate may reduce the formation of these antibodies. The significance of these differences between the three agents is unknown in RA, unlike the situation with Chron’s disease, in which a definite difference in efficacy of Infliximab and etanercept has been shown.
These agents are also used in other diseases and showed a good response in such as Behcet’s disease, especially the eye involvement (uveitis), reactive arthritis and herniated disc.

Guide lines for the use of TNF-blockers in RA are different from country to country and from one institution to another as this depends on the availability of these agents and financial considerations. The guidelines for the use of TNF blockers in RA patients requires the failure of one or two disease modifying anti-rheumatic drugs (DMARDS), one being methotrexate for at least three months (9,10,11,12,13), and these are the guidelines that we follow for our RA patients.

Ankylosing spondylitis patients should fail two non-steroidal anti-inflammatory drugs (NSAIDs) each for three months before being eligible for TNF blockers. They should also have an activity index of more than four using the Bath ankylosing spondylitis activity index (BASDI) (14,15,18).

TNF-Blockers are approved for the treatment of psoriasis and psoriatic arthritis either alone or in combination with DMARDs (16,17,18).

Although there have been no head-to-head trials, the three anti-TNF agents appear to have similar efficacy with up to 70% of patients achieving at least a 20% improvement in disease activity (ACR 20) with the first TNF blocker (9,13).

Our data shows that 62.2% of the patients used etanercept in comparison to 26.8% who used infliximab and 26.8% who used adalimumab. The reason for this difference in the use of these different anti-TNF agents was the availability of these agents at our institution.

The response rate was around 82% in the non-switchers compared with the published data of 70% for RA, as in PSA and AS they had almost complete response, as they were the first users of TNF blockers.

Switching from one TNF blocker to another one was either because of lack of response or to an adverse drug reaction. We do not have the results of the patients who switched to TNF blockers long term.

There are numerous reports in which it has been suggested that initiating therapy with a second anti-TNF blocker in patients who failed therapy with a first agent (due to lack of efficacy or because of an adverse event) may be beneficial and not associated with an increased rate of adverse event with the second agent (19-27).

Regarding the side effects, the rate of infection was not different from the published data (8), AS bacterial infections or reactivation of TB are the most common. Three out of 82 patients had infections and required antibiotic treatment but only one of them required intravenous antibiotics and admission to the hospital.

Active tuberculosis (TB) that, in most instances, is the result of re-activation of latent TB infection has been associated with the treatment of tumor necrosis alpha blockers (28-31) and different recommendation for targeting patient’s latent TB infection have been proposed by scientific organization, health authorities, and other experts worldwide to decrease the risk of active TB. In our cohorts all patients who received TNF-blockers had a screening in the form of a PPD skin test and chest x-ray. In the general population latent tuberculosis is diagnosed when the induration in the PPD skin test is 15mm or above; a reaction of 10 mm or above is positive in a population with a history of definite or probable exposure to TB, and 5 mm is the threshold for an immunocompromized population. Latent TB should be treated with a nine month course of isoniazide 300mg/day.

Of 82 of our patients screened for TB, only one had a positive PPD skin test and required prophylactic treatment before starting TNF-blockers with no subsequent reactivation despite our being in a likely endemic area for tuberculosis because of the large immigrant population.

One patient with reactive arthritis in the form of tendinitis, who failed DMARDS, was treated successfully with Adalimumab as has been reported in the literature (18).

Also we treated successfully one patient with uveitis secondary to Behcet’s disease with Infliximab infusion as in published data sight-threatening uveitis in patients with Behcet’s disease has successfully treated with infliximab (32)

Our data could be criticized as being retrospective, concerning a small number of cases and not measuring disease activity by ACR or DAS disease activity scores; also we did not check for anti-CCP antibodies as it was not available in early 2001 at our institution. On the other hand our data reflect the daily practice in the rheumatology out patient clinic in Qatar following international guidelines in the management of inflammatory arthritis and other rheumatological condition and we expect that the small sample reported here will increase considerably in the future.

References:


QATAR MEDICAL JOURNAL | VOL. 18 / NO. 1 / MAY 2009
The use of TNF Blockers in the Rheumatology...


