REPORT

Biological drug use: US perspectives on indications and monitoring

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An estimated 20% of patients with rheumatoid arthritis (RA) receive tumour necrosis factor (TNF) inhibitor treatment. This paper presents the results of an online survey of US rheumatologists (1023 respondents) conducted in April 2005 on issues relating to use of TNF inhibitors in RA. The primary determinant of TNF inhibitor use among the participating rheumatologists was physician preference rather than patient preference or payor guidelines. Qualitative (rather than quantitative measures) assessments (physician overall assessment, symptom review, etc.) and laboratory measures were more frequently employed when assessing and treating patients with RA. Clinical assessments with hepatic enzymes and complete blood count as an additional safety tool were most commonly employed to monitor drug safety. Nearly all the rheumatologists (≥92%) felt that a partial purified derivative (PPD) test was indicated when using a TNF inhibitor, but were equally split with regard to those with a history of PPD positivity or BCG vaccination. The frequency of serious adverse events was estimated and included tuberculosis, systemic fungal infection, demyelinating disorders, cytopenia, drug induced lupus, lymphoma, and hepatic failure. Among 454 RA patients who became pregnant while receiving biological therapy there were 378 normal deliveries, 9 premature babies, 5 therapeutic abortions, and 25 miscarriages. It was concluded that a greater than expected number of US rheumatologists are familiar with biologicals and TNF inhibitor therapies, but uncertainties and educational gaps still exist regarding their use and monitoring.

The past decade has seen biological therapies develop from concept to clinical trials to a widely marketed class of new therapies. Although many candidate biopharmaceuticals have been tested in the autoimmune and inflammatory disorders, only a few are currently available for use.[1 2] Since 1998, three tumour necrosis factor (TNF) inhibitors and one interleukin (IL)-1 inhibitor have been approved for use in rheumatoid arthritis (RA). These agents have slowly been employed in RA, such that less than 20% of patients have received biological therapies. Market research shows that many rheumatologists are familiar with these agents but only a minority use these agents regularly for their patients with RA. For most, the use of TNF inhibitors or anakinra has largely been reserved for those patients who are refractory to multiple disease modifying antirheumatic drugs (DMARDs) or those with advanced and aggressive disease. The diversity of biological usage appears to relate to their ''newness'' and concerns over safety and cost.[3] Nonetheless, worldwide use of TNF inhibitors has been bolstered by their use in other indications (Crohn's enteritis, ankylosing spondylitis, psoriasis) and this class has grown to over US$4 billion in sales. Several new biological agents (for example rituximab, abatacept, tocilizumab) have shown promising results and may be added to our arsenal of drugs to treat RA.

With growing use comes growing concern over who should get these expensive new therapies and, once prescribed, how should these be used in practice? This report will review current answers to these issues and provide insights from a recent survey on the use of these agents among practising US rheumatologists.

METHODS

Available information on indications and use of TNF inhibitors was sought from review of current prescribing guidelines and online searches for ''indications, guidelines for use, and monitoring'' of TNF inhibitors or biologicals. Moreover, an online survey of practising US rheumatologists was conducted in April 2005. An invitation was sent to 2880 US rheumatologists (listed in the American College of Rheumatology (ACR) directory as engaging in ''patient care'') via email. Participants responded during a 30 day period in April 2005. The survey included 33 questions about respondent demographics, their practice habits, impressions regarding the indications/use of biologicals and TNF inhibitors, and safety monitoring and safety concerns. A total of 120 rheumatologists declined the survey, and 1023 provided answers online; thus the total response rate was 40%. Many rheumatologists (>600) responded to the email but not the online survey and indicated their preference to not participate. Reasons for non-participation included: retirement, no longer seeing patients, fellowship, paediatric rheumatology only, no biological experience, and unavailability or personal matters. Although online line surveys are easy to complete and data acquisition is fast, inexpensive, and accessible, these may also be hampered by reporting bias (volunteer effect) and recall bias. The only method we used to minimise this risk was the three time email invitation to non-responders.

RESULTS

Physician/practice characteristics

Responses came from private practice (55%), academic (36.6%), government/military (5.3%), and other (3.1%) groups. Private practice included those from solo practices (17%), group practice (20.5%), and multispecialty groups (17.6%). Most responses came from California (n = 100), New York (n = 88), Texas (n = 82), Pennsylvania (n = 56), and Massachusetts (53). States with a ≥50% response rate included South Dakota, West Virginal, Arizona, Nevada, Vermont, Tennessee, and Texas.

Abbreviations: ACR, American College of Rheumatology; DAS, Disease Activity Score; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; MTX, methotrexate; PPD, partial purified derivative; RA, rheumatoid arthritis; TNF, tumour necrosis factor

Box 1: Relative contraindications for tumour necrosis factor (TNF) inhibitor use

- Systemic lupus erythematosus, lupus overlap syndromes
- Multiple sclerosis, optic neuritis
- Current, active, serious infections
- Chronic, recurrent infections
- Immunosuppression
- History of tuberculosis or positive partial purified derivative (PPD) (either untreated)
- Congestive heart failure
- Pregnancy

The US rheumatologists were represented by more men (72.3%) than women (27.7%). The mean age was 49 years. Practice experience varied, with 18.7% in practice for less than 5 years and 38.2% in practice for more than 20 years (table 1). They saw a mean of 62.4 patients overall (fig 1) and 22 RA patients (fig 2) each week. Based on the frequency and range of responses, the average US rheumatologist sees a mean of 2996 patients per year, including 1059 RA visits per year. Presuming that RA outpatient visits recur every three to four months, the average rheumatologist currently manages between 265 and 353 RA patients in his/her practice. Such patient care is supported by Medicare (35%), health maintenance organisation (22.8%), or preferred provider (21.7%) insurance programmes (table 2).

Table 1 How many years have you been in rheumatological practice?*

Years in practice	Response (%)
Less than 5	18.7
5–10	10.5
10–15	15.5
15–20	17.1
20–25	20.0
More than 25	18.2

*Mean responses (n = 1023). (Online survey, US rheumatologists, April 2005.)

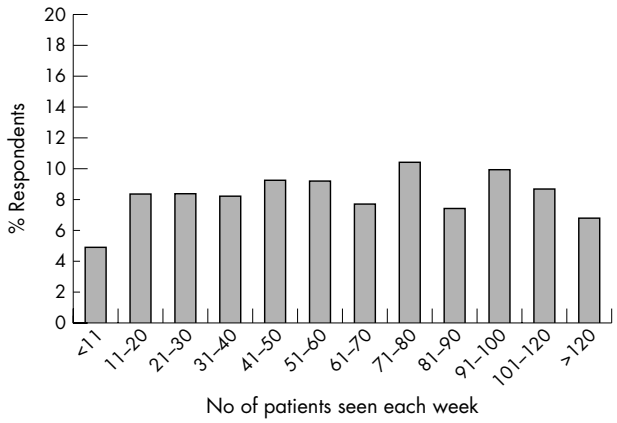

Figure 1 Overall number of patients seen weekly in practice by US rheumatologists (online survey, April 2005).

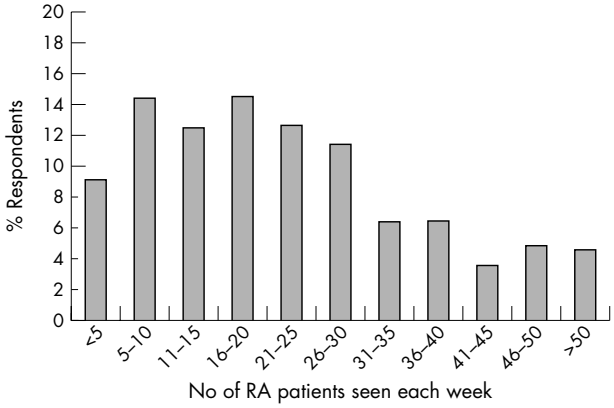

Figure 2 Number of patients with rheumatoid arthritis seen weekly in practice by US rheumatologists (online survey, April 2005).

Indications for use

There are few guidelines or publications that delineate which patient should ideally receive a TNF blocker.[4 5] In fact, there is clearer consensus on who should *not* receive TNF inhibitors (box 1). For nearly all of these drugs, the US Food and Drug Administration (FDA) approved package labelling suggests that biological agents are indicated in RA patients with moderate to severe disease activity after failing methotrexate (MTX) and/or another DMARD(s). The 2002 revised ACR guidelines for the management of RA are less specific about the use of these agents, but do suggest that biological therapies may be considered (along with other combination regimens or monotherapy DMARDs) after an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs), steroids, DMARDs, and MTX.[6] In addition, many insurers and payors and government agencies will require that RA patients have an adequate trial of one or more DMARDs (including MTX). Unfortunately, such rules vary widely and may be influenced by region, state, managed care plan, and employer determined group benefits. Some payors may even require minimal evidence of disease activity (for example number of swollen joints, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)) before approving the use of a TNF inhibitor. While payor, institutional, and published guidelines and prescribing rules do exist, many rheumatologists may not be familiar with these or agree with their stringency.

Nevertheless, the use of TNF inhibitors has grown to encompass nearly 20% of the rheumatoid population. Conversely, a large majority of patients and physicians have never used these agents. Although cost, safety concerns, and prescribing rules are primary impediments to the use of biologicals, other contributory factors limit the use of

Table 2 Please estimate the payor/provider mix in your practice?*

Payor	Response (%)
Medicare	35.0
Health maintenance organisation (HMO)	22.8
Preferred provider	21.7
Commercial	14.9
Medicaid	13.2
Senior HMO	7.8
Private pay	7.5
Charity	6.3
Professional courtesy	1.4
Worker compensation	0.8

*Mean responses (n = 968).

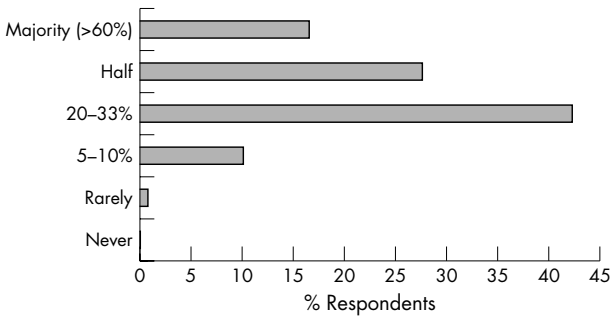

Figure 3 US rheumatologists were asked ''How often do you use TNF inhibitors in RA?'' (online survey, April 2005).

biologicals in the USA. For example, more than half the RA population has never seen a rheumatologist, over a third are uninsured, and the Centers for Disease Control and Prevention (CDC) estimates there are 10.3 million Americans who have chronic joint symptoms but have never seen a physician[7]; hence not all arthritis patients will seek appropriate medical help. There are also many patients and physicians who feel they are currently ''doing well'' on traditional monotherapy or combination DMARD therapy.

When US rheumatologists were surveyed about their use of TNF inhibitors in RA, respondents judged themselves to be frequent users with most (42.3%) claiming use in 20–33% of patients and 44.2% claiming to use these agents in either half or a majority of patients (fig 3). Less than 1% admitted to rarely or never using TNF inhibitors. When asked in how many patients did they prescribe TNF inhibitors in the past 5 years, the mean response was 139.5 (median 100; range 1–3000) patients per rheumatologist. As a group, they have given TNF inhibitors to 119 095 RA patients in the last five years preceding the survey. When asked what or who the primary determinant to TNF inhibitor use was, the favoured response was physician preference (48%), rather than patient preference (20%) or insurance/payor guidelines (21%). Published guidelines (9%) or institution guidelines (1.5%) were seldom influential. Table 3 lists those factors that most influenced the decision to use a TNF inhibitor. Foremost among these were failure of either MTX or multiple DMARDs, physician assessment, functional impairment, and radiographic worsening or erosions. Although the vast majority admitted certain requirements must be met (for example 42% said they must fail MTX first), 15.5% stated there are no current restrictions on the use of TNF inhibitors in their area.

Table 3 Factors that most influence the decision to use a TNF inhibitor*

	Response (mean)
Failure of methotrexate	1.46
Failure of multiple (>2) disease modifying antirheumatic drugs (DMARDs)	1.50
Physician global assessment	1.56
Radiographic erosions or worsening	1.58
Functional impairment	1.59
Extra-articular manifestations	2.38
Published guidelines	2.56
Formulary restrictions	2.67
Patient request	2.82
Managed care guidelines	3.24
Director consumer advertising	4.34

*Respondents were asked to rank these on a scale of 1–5 from most influential (1) to least or never influential (5) (n = 953). (Online survey, US rheumatologists, April 2005.)

Although payor guidelines and managed care was felt to be modestly influential (table 3), 61% of surveyed rheumatologists felt that managed care did place significant restrictions on the use of TNF inhibitors, and 30% of these felt that restrictions were getting worse. The influence of payors and managed care was further queried by asking about the use of rituximab (commercially available but not FDA approved for use in RA) in RA and the use of TNF inhibitors in diseases other than RA. Although 59% had never used rituximab in the treatment of RA, the remaining US rheumatologists had treated a mean of 4.4 RA patients and wanted to treat another 4.3 RA patients with rituximab. However, 1.9 patients had rituximab denied by payor or insurance carrier. Reasons for rituximab denial included: an unapproved indication (68%), non-formulary drug (16%), insufficient proof of need (10%), and cost (6%).

TNF inhibitor use has expanded to other inflammatory disorders, with Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and psoriasis being either approved indications or indications under investigation for approval. Table 4 shows that although most rheumatologists can easily prescribe TNF inhibitors in ankylosing spondylitis, psoriatic arthritis, and psoriasis, nearly a third require a letter of medical necessity. For 50–60% of rheumatologists in the survey, patients with inflammatory eye disease, Behçet's, or sarcoidosis were possible or probable recipients of TNF inhibitors (with a supportive letter), yet 20–30% stated these would be difficult to get approval for. Also, most rheumatologists had an aversion or were unlikely to use TNF inhibitors in Wegener's granulomatosus, polyarteritis nodosa, giant cell arteritis, and systemic lupus erythematosus.

Monitoring

Successful long term use of TNF inhibitors and other biological agents will require ongoing monitoring to confirm efficacy (and continued need) and avoid drug toxicity. In the present survey, rheumatologists were asked to rank those measures most useful in documenting therapeutic benefit and ongoing need (table 5). Measures that were ''most important'' for continued use included the physician joint examination (53%), physician assessment of disease activity (48%), patient response (47%), and drug tolerability (41%). A third judged ESR or CRP and radiographs to be ''frequently important'', but 41% stated that functional outcomes and 62% stated that the Disease Activity Score (DAS) was rarely, or never, important in such assessments.

Rheumatologists were also asked about what practice measures they commonly employed in the care of patients

Table 4 How easy or hard is it to prescribe a TNF inhibitor for the following conditions? (Would a letter of necessity or phone call to a medical director be necessary?)*

	Response (%)			
	Easy; no letter	Probable/ possible with letter	Unlikely or Impossible	I would never use in this condition
Ankylosing spondylitis	57	31	3	0
Psoriatic arthritis	65	34	1	0
Psoriasis	45	43	4	8
Uveitis/episcleritis	10	60	20	9
Behçet's	7	54	28	11
Sarcoidosis	6	50	29	15
Polyarteritis nodosa/ giant cell arteritis	5	41	32	22
Wegener's	5	41	25	28
Lupus	5	31	21	42

*n = 955 (online survey, US rheumatologists, April 2005).

Table 5 Factors used to assess efficacy and need for ongoing TNF inhibitor therapy*

	Response (mean)
Physician joint examination	1.69
Patient assessment of response	1.88
Drug tolerability	2.04
Physician global assessment	2.14
Radiographic assessments	2.94
Erythrocyte sedimentation rate or C-reactive protein	3.18
Functional outcome measures	4.20
Disease Activity Score (DAS)	5.41

*n = 880 (online survey, US rheumatologists, April 2005). Respondents were asked to rank these on a scale of 1–8 from most important (1) to never important (8).

with RA. There were few differences in the care of all patients with RA and the subset being started on TNF inhibitors (table 6). Although sedimentation rate values (79.8%) and CRP (68.3%) were frequently checked, and tuberculin skin tests (that is, PPD) (59.1%) frequently performed in patients receiving TNF inhibitors, serum rheumatoid factor (16.4%) and anticyclic citrullinated peptide (anti-CCP) antibodies (12.2%) were less frequently checked. It appears US rheumatologists rely heavily upon qualitative assessments (physician overall assessment, symptom review, morning stiffness, and complaint focused joint examinations) and laboratory measures (complete blood count, ESR, CRP, hepatitis screens, antinuclear antibodies) when assessing and treating patients with RA. The quantitative measures that comprise validated outcome tools (28 joint tender and swollen joint counts; physician and patient global assessments; functional measures) are less commonly employed. Radiographs were variably performed, as nearly three-quarters stated that they will take baseline films, half will perform yearly hand radiographs and a quarter will routinely take feet radiographs. Uncommonly used measures included a scored Health Assessment Questionnaire (HAQ) (12.3%), magnetic resonance imaging (MRI) (5–8%), joint ultrasound (1–2%), DAS (6%), or an ACR 20 (or ACR-N) outcome (1.8%).

Table 6 Which of the following do you usually collect or perform in your RA patients?*

	Investigation performed (%)	
Measure	Routine RA care (n = 978)	RA patient started on TNF inhibitor (n = 892)
Vital signs	95.5	ND
Physician overall assessment	ND	83
Full blood count	92	81.5
Symptom review	91.9	ND
Morning stiffness	88.8	87.7
Baseline radiographs	75.4	ND
Joint examination (complaint focused)	72.8	74.7
Erythrocyte sedimentation rate	68.1	79.8
C-reactive protein	51.8	68.3
Tuberculin skin test (PPD)	48.3	59.1
Yearly hand radiographs	48.3	51.1
Hepatitis C antibody	45.9	ND
Patient global assessment VAS	45.3	39
Patient questionnaire	45	39.3
Antinuclear antibody	44.6	ND
Patient pain VAS	43.7	50.9
Physician global assessment VAS	41.9	31.8
Rheumatoid factor	38.3	16.4
Hepatitis B surface antigen	36.4	ND
Cyclic citrullinated peptide antibody	27.2	12.2
Yearly feet radiographs	27.1	23.4
28 joint count (TJC, SJC)	27.1	27
66 joint count (TJC, SJC)	18.8	20.4
HAQ (unscored)†	17.7	14.8
HAQ (scored)†	12.3	16.3
Yearly chest radiograph	16.3	20.6
Magnetic resonance imaging	8.2	5.2
Ultrasound	1.9	1.1
Pregnancy test	7.4	7.3
DAS‡	6	6.5
ACR 20 or ACR-N	1.8	2.8

*The table presents the results of two questions wherein the difference was the type of patient (RA v TNF treated RA patient). (Online survey, US rheumatologists, April 2005.)
†Includes any version of the HAQ (mHAQ, MD-HAQ, Clin-HAQ, etc.).
‡Includes any version of the Disease Activity Score (DAS 28, DAS 44, DAS-CRP, etc.).
CCP, cyclic citrullinated pepaide; HAQ, Health Assessment Questionnaire; ND, no data; PPD, partial purified derivative; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Monitoring for drug safety is a core concern for all rheumatologists. When assessing safety in patients on TNF inhibitors, the rheumatologists in the survey primarily relied on clinical assessments (history, physical examination) (92%) and used hepatic enzymes (69%) and complete blood count (77%) as an additional safety tool (fig 4). While nearly 20% stated they never undertook cancer screens or serological examinations (antinuclear antibody (ANA), dsDNA), most admitted to undertaking serological examinations (78%), cancer screens (82%), and chest radiographs (76%) when clinical signs or symptoms warranted such investigations. When asked how often serological examinations (ANA, dsDNA) are done in patients receiving TNF inhibitors, most (57%) did these in patients with signs of lupus (58%), with fewer doing these before drug initiation (14%), or yearly (9%) or every six months (9%), and 12% never did serological testing.

When asked to judge how often (if ever) a tuberculin skin test (or PPD) was needed with various DMARDs, nearly all (≥92%) rheumatologists felt that a PPD was indicated when using a TNF inhibitor (table 7). Surprisingly, nearly 40% felt that PPD testing was sometimes done when using MTX or combination DMARDs, and 65% felt PPD testing was always or sometimes required with high dose steroids. It is uncertain if these results reflect what is actually done in practice as earlier questions revealed that fewer (55–68%) did a PPD when clinically warranted, 21–37% did a PPD every

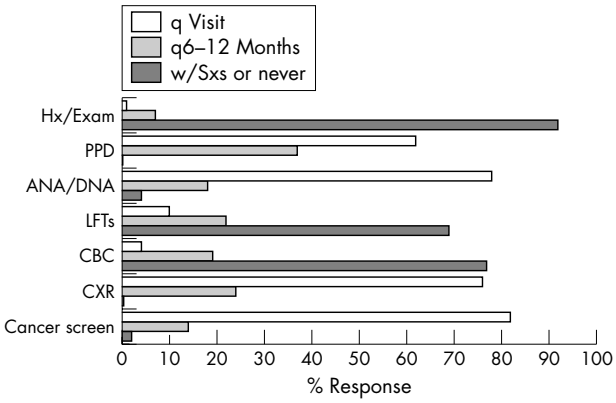

Figure 4 Measures and frequency of safety assessment by US rheumatologists among patients receiving biological drugs (online survey, April 2005). ANA, antinuclear antibody; CBC, complete blood count; CXR, chest radiograph; Hx, history; LFT, liver function test; PPD, partial purified derivative; q, every; w/Sxs, only when presenting with symptoms.

Table 7 How often do you routinely perform tuberculin skin testing with this drug or situation?*

	Response (%)				
	Always	Sometimes	Never	Don't use this drug	Don't know
Etanercept	93	5	2	0	0
Infliximab	95	3	1	1	0
Adalimumab	92	4	2	2	1
Anakinra	42	13	15	28	2
Rituximab	35	6	10	39	9
Abatacept	18	1	2	67	12
Methotrexate	8	39	51	0	1
Combination DMARDs	9	41	48	1	1
High dose steroids	17	48	33	1	1
History of PPD+	28	21	47	1	4
History of BCG vaccination	22	23	45	2	7

*Respondents asked to choose one answer (column) for each drug (n = 900, online survey, US rheumatologists, April 2005).
BCG, bacillus Calmette-Guérin; DMARD, disease modifying antirheumatic drug; Hx, history; PPD, partial purified derivative.

12 months, and 7% claimed to never do this test. These responses correlate with prior questions (table 6) indicating 48–59% of rheumatologists do PPD testing in their RA patients. There were diverse answers with regard to whether PPD is indicated with other biologicals. Although many (28–67%) did not use (or were not familiar with) anakinra, rituximab, or abatacept, 42%, 35%, and 18% respectively judged PPD testing to be needed. They were equally split on whether a PPD was indicated in those with a history of PPD positivity or BCG vaccination: 45–49% favoured testing and 45–47% never performed PPD in these situations. Further education, familiarity with the CDC guidelines,[8] and review of prescribing information in the packaging guidelines for these agents would resolve these issues.

Although TNF inhibitors are likely to be held in the setting of serious infections, this survey revealed other unique situations of concern to the rheumatologists. TNF inhibitors were suspended by 91–98% of rheumatologists in the presence of serious infections (septic arthritis, pneumonia, cellulitis) and worsening of congestive heart failure (fig 5). Although the relation between this class of drug and herpes zoster infection is not established, over 82% of the surveyed rheumatologists held anti-TNF therapy with a shingles outbreak. Two thirds held the drug for any fever, sinusitis, or urinary tract infection; half for hospitalisation or large injection site reactions; but only a third for an upper respiratory infection. Suspension of biological therapy might also be considered before elective major surgery (for example joint replacement or hysterectomy). When asked how long before major surgery would they suspend TNF inhibitor therapy, the rheumatologists' mean response was 4 weeks for infliximab, 2.5 weeks for adalimumab, and 1.7 weeks for etanercept. Although there are no guidelines for such action, a recent abstract suggested suspension of drug treatment should be considered as their cohort study showed a fourfold higher risk of postoperative infections in those taking TNF inhibitors.[9]

Table 8 How often have you encountered these adverse events that you ascribed to a tumour necrosis factor (TNF) inhibitor? (US rheumatologists online survey, April 2005)

Adverse event	Never seen (%)	1–3 cases (%)	Calculated total events	Event risk per patient (%)
Pneumonia	19	42	2720	2.28
Herpes zoster	35	45	1847	1.55
Sepsis	42	45	1436	1.21
PPD positivity	56	30	1340	1.13
Tuberculosis	78	21	423	0.36
Systemic fungal	76	23	450	0.38
Cytopenia	48	42	1315	1.10
Demyelinating disorder	74	25	463	0.39
Drug induced lupus	56	37	1038	0.87
Vasculitis	76	21	518	0.43
Heart failure	61	33	841	0.71
>3-fold increase hepatic enzymes	74	21	608	0.51
Hepatic failure	97	2	61	0.05
Lymphoma	76	22	426	0.36
Leukaemia	97	3	93	0.08
Solid tumor	69	25	787	0.66
Pregnancy on TNF inhibitor	77	21	493	0.41
Bronchospasm	68	24	906	0.76
Hypotension	55	31	1374	1.15
Severe skin reaction	42	42	1593	1.34
Cardiac arrest	98	2	40	0.03

Adverse events

Respondents were asked to estimate the relative frequency of adverse events among TNF inhibitor treated patients in their practice (table 8). Many had one or more cases of serious infections (pneumonia, sepsis, herpes zoster), severe skin reactions, hypotension, cytopenia, and PPD positivity in their patients taking biologicals. Severe drug reactions

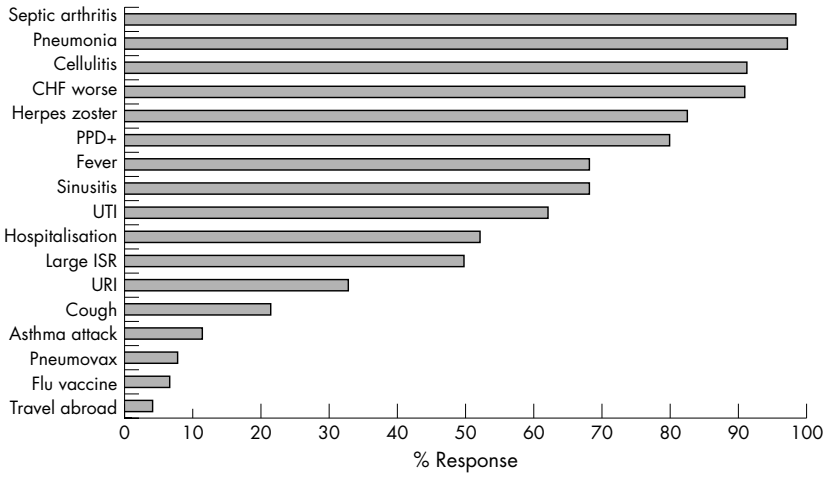

Figure 5 Conditions in which US rheumatologists suspend use of tumour necrosis factor inhibitors (online survey, April 2005). CHF, congestive heart failure; ISR, injection site reaction; PPD, partial purified derivative; URI, upper respiratory infection; UTI, urinary tract infection.

(bronchospasm, hypotension, skin reactions) occurred in 0.76–1.34% of patients on TNF inhibitors. Estimated total cases of serious adverse events of interest included data on tuberculosis (n = 423), systemic fungal infection (n = 450), demyelinating disorders (n = 463), cytopenia (n = 1315), drug induced lupus (n = 1038), lymphoma (n = 426), hepatic failure (n = 61), and pregnancy (n = 493). Rare (<0.1%) events included leukaemia (0.08%), hepatic failure (0.05%), and cardiac arrest (0.03%).

Pregnancy, RA, and TNF inhibitors

TNF inhibitors carry a class "B" pregnancy risk, suggesting that although no risk is apparent from animal studies, there are no controlled studies of women receiving these agents. There are reports of favourable pregnancy outcomes among women subjected to TNF inhibitor therapy, but these are few.[10] The present survey asked US rheumatologists how many of their RA patients on TNF inhibitors became pregnant or took these agents during pregnancy. While the previous question estimated 493 pregnancies (see Adverse events above), this question revealed 454 RA patients who became pregnant while receiving biological therapy. Surprisingly this included 142 patients (31.3%) who required TNF inhibitor therapy throughout the pregnancy. There were 378 normal deliveries, 9 premature babies, 5 therapeutic abortions, and 25 miscarriages in this group. There were no reported birth defects, fetal malformations, or neonatal deaths. Three children were said to be born with medical problem(s) due to the TNF inhibitor, but no additional information was provided.

RECOMMENDATIONS

Although this review of current practices demonstrates a higher than expected number of US rheumatologists familiar with biologicals and TNF inhibitor therapies, uncertainties and educational gaps still exist regarding their use and monitoring.

Indications and use of TNF inhibitors

There is an evidence based and widely held consensus that all RA patients should be treated with MTX—the current standard of care. This is supported by recent trials[11–13] that indicate the margin of clinical benefit of a TNF inhibitor over MTX is modest or absent. Nonetheless, there is a significant radiographic benefit (table 9) afforded by the TNF inhibitors. Thus these agents should be used in patients at greatest risk for aggressive disease, and TNF inhibitors should be a strong and early consideration in patients with an aggressive phenotype (many joints, functional impairment, seropositivity for rheumatoid factor or CCP, elevated ESR or CRP, radiographic erosions). Otherwise, TNF inhibitors may be useful in those not responding to MTX or other DMARDs. There is strong evidence to also support their use in ankylosing spondylitis patients with axial involvement and psoriatic arthritis.

Monitoring and safety

There is a slowly growing demand in the USA to document the efficacy of biological therapies. However, current rheumatological practices are not uniformly capable of meeting this need. US rheumatologists will need to better document response and safety by employing validated outcome tools that can be adapted for clinical practice, including the HAQ, DAS, and Simplified Disease Activity Index (SDAI) score.[14] The ACR 20, and its derivations, is not a suitable tool for clinical practice and should remain as it was intended—a clinical trial outcome measure. Avoidance of drug toxicity will best be accomplished by proper patient selection (see box 1), inception tuberculin skin testing (with yearly repeats in high risk individuals) and vigilant concern and close observation for rare and serious adverse events associated with the use of TNF inhibitors (table 8). Lastly, there is a major need for infection management guidelines and population based studies that will delineate who should not receive biological therapies and when they should be suspended or for how long.

Table 9 The difference between methotrexate and TNF inhibitors responses: where is the margin of benefit at 52 weeks*?

Clinical trial	Clinical endpoint ACR 20 response (%)			Radiographic endpoint No radiographic progression (%)		
	MTX	TNFi	Margin†	MTX	TNFi	Margin†
TEMPO	75	76	+1	57	68	+11
ERA	65	72	+7	60	72‡	+12
ASPIRE	54	62	+8	45	58	+13
PREMIER	63	54	−9	37	51	+14

*Results from references 11–13
‡No progression in erosion score.
†Margin of benefit = TNFi result − MTX result.
ACR, American College of Rheumatology; MTX, methotrexate; TNFi, tumour necrosis factor inhibitor.

Competing interests: none declared

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