Long-term use of adalimumab in the treatment of rheumatic diseases

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Abstract: Adalimumab, a fully humanized monoclonal antibody against tumor necrosis factor-alpha (TNFα), has been evaluated in various randomized placebo-controlled trials in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis. In the short time frame of these trials adalimumab has been shown to be effective in reducing disease activity, slowing radiographic disease progression and improving patients’ quality of life, while at the same time demonstrating an acceptable safety profile. Furthermore, release of adalimumab on the market, prospective observational studies, as well as open-label extensions of the original double-blind trials have provided experience and data about the long-term efficacy and safety of the drug. Initial effectiveness, in terms of reducing disease activity, is sustained, while in most cases patients treated with adalimumab experienced a slower radiographic progression and consequently less disability and improved health-related quality-of-life outcomes. Moreover, long-standing treatment of thousands of patients with adalimumab outside the controlled context of clinical trials was not related to new safety signals, with the most common adverse events being respiratory infections. The most common serious adverse events seem to be tuberculosis reactivation, while a putative association with malignant lymphoma development is not yet proven. Besides, both of these adverse reactions pertain to the whole TNFα blocker group. In conclusion, adalimumab is a safe and effective option for the treatment of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis.

Keywords: adalimumab, tumor necrosis factor-alpha, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis

Introduction

Great advances in the treatment of chronic autoimmune inflammatory arthritides, concerning both therapeutic concepts and means, have marked the last two decades. In the 1990s the inversion of the classical “therapeutic pyramid” for the treatment of rheumatoid arthritis (RA) became mainstream in rheumatology practice, while later the concept “treat early to treat effectively” was realized as a necessity in order to achieve favorable outcomes in RA both in the short and long term. Concerning medications methotrexate (MTX) was regarded as the “anchor drug” for the treatment of RA, while other disease-modifying anti-rheumatic drugs (DMARDs) such as cyclosporine A and leflunomide were recruited or developed to add further therapeutic benefit against chronic inflammatory arthritis as monotherapy or in combination.

Despite the implementation of these new therapeutic concepts and agents there were issues still to be addressed. A considerable proportion of patients with RA could experience no significant benefit: for example in randomized controlled trials in early RA, 35% of
patients receiving MTX monotherapy failed to achieve a 20% American College of Rheumatology (ACR) response at year 1 and 44% at year 2,6,7 while in initial aggressive therapy groups ACR20 failure rates around the sixth month were 20% to 28%.8,9 In patients responding to treatment, remission rates were not satisfactorily high with ACR70 response rates at years 1 and 2 not exceeding 30% with MTX monotherapy,6,7 while it was realized that despite clinical remission structural damage progressed10 causing disability in the long term. Moreover in seronegative spondyloarthritides axial involvement is generally regarded unresponsive to DMARDs.11,12 Finally, adverse events have been another significant parameter curtailing the use of classic DMARDs.13

On the other hand, recent advances in molecular and cellular biology shed light in mechanisms of rheumatic diseases revealing the role of specific molecules, such as tumor necrosis factor-alpha (TNFα),14-16 interleukin (IL)-1, IL-6, IL-17, IL-23, immune cell co-stimulation pathways and the role of specific immune cell subsets, such as Th1, Th2, Th17, T regulatory cells, B cells and dendritic cells. Taking advantage of genetic engineering techniques and the monoclonal antibody technology the new knowledge led to the development of molecules targeting specific pathogenic cytokines (TNFα, IL-1, IL-6), T-cell co-stimulation pathways associated with the cytotoxic T lymphocyte antigen-4 (CTLA-4) and even B-cells, thus launching the era of targeted therapies in rheumatology.

At the time of writing, three TNFα blocking agents (infliximab, etanercept, adalimumab) had been licensed for use in patients with RA, psoriatic arthritis (PsA) and anklyosing spondylitis (AS), while etanercept and adalimumab had also been approved for use in active polyarticular juvenile idiopathic arthritis (JIA). Anakinra (recombinant human IL-1 receptor antagonist) has been approved for use in patients with RA with poor response to classic DMARDs. Further, two other molecules, rituximab (murine-human chimeric monoclonal antibody against B-lineage cells expressing the CD20 molecule) and abatacept (CTLA-4-Ig fusion protein) have been released for the treatment of RA. Abatacept has also been approved in the United States for use in active polyarticular JIA.

The integration of biologics in everyday rheumatology practice did not prove to be a panacea though, as their shortcomings were similar to those of the older classic DMARDs. For example, in MTX-naïve patients with early RA etanercept or adalimumab monotherapy were no more effective than MTX monotherapy after 1 year of treatment. Actually in both cases it was the combination of MTX and TNFα blocker that was more efficacious comparing to each drug alone.5,7,17 In patients responding to biologics different matters subsequently emerged. One of them is persistence of efficacy in the long term.18-23 Another issue is whether biologics actually possess “disease-modifying” properties preventing further disease progression and structural damage24-27 and even allowing for drug cessation at some point in time. If the goal is not merely to treat, but to cure rheumatic diseases, could this be achieved using biologics and, if so, when is the appropriate time for them to be used, so as to modify the disease, and how long should they be used for this purpose?28 If there is actually a window of opportunity in RA, then long-term results regarding patients treated all from the beginning with biologics (as in group 4 of the BeSt study)29 will provide insight into this matter.

On the other hand, in PsA and AS anti-TNFα agents have produced satisfactory outcomes, even better than in RA.30-35 Long-term data on efficacy are still limited though,36-41 while the impact of these drugs on radiographic damage seems to vary with more pronounced effects in peripheral than axial joints.42-45 Another issue is the time length of treatment, since there is evidence that cessation of treatment leads to disease relapse.46,47

As regards the safety of TNFα blockers, whereas initial screening and a high degree of suspicion have reduced the occurrence of severe, particularly mycobacterial infections,48 the risk of malignancy in the long term is an emerging and still unresolved issue.49-54 Further, induction of autoimmunity,55,56 neurologic disease,57-59 effects on metabolic parameters60-64 and the cardiovascular risk65 are issues not yet investigated thoroughly. If rituximab carries the experience of almost 12 years of use in hematologic patients, safety observations regarding these patients cannot be simply extrapolated to the rheumatologic population, while long-term efficacy and safety data concerning abatacept are still limited.66,67 Prospective observational studies and drug safety registries are probably the appropriate settings to monitor safety in the long term and in “real life” patients, such that are usually not eligible for the efficacy-assessing randomized controlled trials.

Finally, biologic drugs are far more expensive than older DMARDs and long-term cost-effectiveness in a socioeconomic perspective is certainly an issue concerning the health system policies in modern societies where resources are not infinite.68-70

In this review we will discuss the results of the major adalimumab clinical trials, as well as observational studies in
rheumatic diseases with a focus on the long-term effectiveness and safety of adalimumab in RA, AS, PsA and JIA. However, we did not systematically review the literature, or formally assess the quality of the studies cited.

Adalimumab

Adalimumab is currently indicated for the reduction of signs and symptoms of adults with moderately to severely active RA, despite the use of DMARDs, including MTX; also for MTX-naïve adults with severe, active progressing RA. In RA patients, adalimumab may be administered in combination with MTX or without MTX, if the latter is contraindicated or poorly tolerated. Moreover, adalimumab is indicated for the treatment of adults with active progressing DMARD-resistant PsA, as well as adults with severe active AS with a poor response to conventional therapy. It is also indicated, in combination with MTX or as monotherapy (in cases MTX is contra-indicated) for the treatment of severe active polyarticular JIA resistant to at least one DMARD. The recommended initial dose for all adult indications is 40 mg administered subcutaneously (sc) every other week (qow).

Pharmacodynamics and pharmacokinetics

TNFα is a cytokine central to a complex network of cells and mediators operating in inflammation and in particular in the pathogenesis of chronic inflammatory arthritis: directly or indirectly it promotes migration of inflammatory cells, activates inflammatory and joint parenchymal cells and induces the production and release of other pro-inflammatory cytokines and metalloproteinases propagating the inflammatory process and tissue damage.71

Adalimumab is a full-length bivalent monoclonal IgG1-κ antibody with a molecular weight of 150 kD targeting specifically TNFα (both soluble [sTNFα] and membrane-bound mTNFα)). Developed with a phage display technique and produced in a Chinese hamster ovarian cell line, it consists completely of human IgG1-κ sequences and is indistinguishable from human IgG1.72 It binds 2 sTNFα molecules, having even the potential to form multimeric complexes, thus preventing sTNFα from binding to the natural TNFα receptors (p55/CD120a and p75/CD120b). Alternatively adalimumab binds 2 mTNFα molecules with the potential of cross-linking and reverse intracellular signaling.71 Adalimumab does not bind lymphotoxin. Adalimumab may thus mediate its actions through various mechanisms: direct neutralization of sTNFα and mTNFα, apoptosis and cytokine suppression through reverse mTNFα-mediated signaling, antibody-dependent cell-mediated cytoxicity and complement-dependent cytotoxicity directed against cells expressing mTNFα (Figure 1).71

When given to patients with RA, adalimumab increases total TNFα levels probably reflecting the formation of TNFα-adalimumab complexes, reduces p75 and p55 soluble TNF receptor levels, reduces IL-1β mRNA expression, reduces IL-6 and IL-1 receptor antagonist levels, reduces metalloproteinase levels (such as pro-MMP-1, pro-MMP-3, MMP-1, MMP-3), reduces cartilage and synovium turnover markers and increases the percentage of memory CD8+ and CD4+ T cells and CD19+ B cells.73

As regards pharmacokinetics, after a single 40 mg subcutaneous injection of adalimumab to healthy adults its absorption is slow with a maximal serum concentration of 4.7 ± 1.6 µg/mL attained after 131 ± 56 h. The average absolute bioavailability is 64%. After a single intravenous dose of 0.5 to 10 mg/kg of adalimumab serum concentrations parallel the dose administered.74

After a single intravenous dose ranging from 0.25 to 10 mg/kg to RA patients the volume of distribution ranged from 4.7 to 6 L, the drug clearance was 12 mL/h, and the mean terminal half-life was almost 2 weeks. Adalimumab concentrations in the synovial fluid of RA patients were 31% to 96% of serum concentrations.74

In adult patients with RA receiving a 40 mg subcutaneous injection of adalimumab qow the mean steady-state trough serum level was 5 µg/mL, which increased to 8 to 9 µg/mL in case of concomitant MTX. MTX reduced adalimumab clearance by 29% and 44% after a single or multiple doses respectively. The mean steady-state trough serum levels of adalimumab were proportionate to the dose administered (20, 40 and 80 mg qow or weekly). In the long term there has been no evidence of change in the adalimumab clearance over at least 2 years.74

In PsA patients receiving 40 mg adalimumab subcutaneously qow the mean steady-state trough serum levels of adalimumab were 8.5 to 12 µg/L and 6 to 10 µg/L with or without MTX respectively, while in AS patients pharmacokinetics was similar to RA patients.74

In RA patients, population pharmacokinetics analyses revealed an increased apparent clearance of adalimumab in the presence of anti-adalimumab antibodies (AAA) and minor increases in patients receiving a lower dose than the recommended one and in the presence of high titers of rheumatoid factor or C-reactive protein (CRP). A trend towards
A lower clearance with increasing age has been observed in RA patients 40 to over 75 years old. No influence of gender on pharmacokinetics could be seen, after adjustment for body weight. Three AAA studies in patients with RA receiving adalimumab with or without concomitant DMARDs showed that AAA develop more often in the absence of concomitant DMARDs, and are associated with lower serum adalimumab concentrations and with poorer clinical response.

**Clinical and radiological efficacy**

Since 1998, when the first results from phase I trials of adalimumab in RA patients were announced at the annual American College of Rheumatology meeting, its long-term efficacy has been investigated in several studies in all of its currently approved indications in rheumatology (Tables 1, 2).

**Rheumatoid arthritis**

Short-term (6 to 12 months) efficacy and safety of adalimumab in RA has been investigated in 5 multicenter randomized controlled trials, 4 of them with established RA and one with early RA and comprising 2869 patients overall. The results of these trials (summarized by Voulgari and Drosos) indicate superiority of adalimumab versus placebo or adalimumab in combination with conventional DMARDs versus conventional DMARDs only, in terms of clinical and radiographic efficacy and an acceptable safety profile. The earliest long-term data derive from open-label extension of the...
an initial phase I study. In this study, 59 RA patients with an inadequate response to MTX were given additional adalimumab initially at various doses, and, during the second year, at a dose of 40 mg every other week or monthly and were followed up for overall 26 months. At the end of follow-up almost 60%, 45% and 30% of patients achieved ACR20, ACR50 and ACR70 responses respectively, similar to the response rates achieved at 6 months already (~62%, 42%, 20% respectively).

These preliminary results were confirmed in the extension of the ARMADA trial and of the DE019 study, as well as in the PREMIER study. In the ARMADA trial, 271 patients with established RA were randomized to adalimumab 20 mg, 40 mg or 80 mg subcutaneously qwq plus MTX or placebo plus MTX for 24 weeks. Of these patients 262 continued in an open-label extension phase receiving a combination of adalimumab (40 mg qwq) plus MTX and were followed up for a maximum of 4 years. Although 228, 207, 186 and 168 patients completed year 1, 2, 3 and 4 of the study, complete clinical data were available for 176, 196, 176 and 147 patients at the respective time points. Whereas the ACR20/50/70 response rates of the adalimumab 40 mg group at 6 months were 67.2%, 55.2%, 26.9% respectively, ACR 20/50/70 response rates at year 1 were 78%, 55%, 31%, at year 2 79%, 54%, 33%, at year 3 77%, 58%, 32% and at year 4 78%, 57%, 31% respectively, showing a sustained efficacy of the combination of adalimumab and MTX over 4 years. Furthermore, disease remission (defined as 28 joint count Disease Activity Score [DAS28] < 2.6) was achieved by 34% of patients at year 1, 38% at year 2 and 43% at year 4, while mean DAS28 values were 3.2, 3.1, 3.1 and 3.0 at the respective time points. Similarly sustained efficacy was seen as regards joint counts and CRP values. Among patients on corticosteroids more patients were able to reduce the dose or discontinue corticosteroids and only one patient had the corticosteroid dose increased, whereas more patients could reduce their MTX dose than increase it. MTX and corticosteroid dose reductions were not associated with worsening of the disease activity measures.

In the DE019 trial, 619 patients with established RA refractory to MTX were randomized to receive adalimumab 40 mg qwq or adalimumab 20 mg weekly or placebo for one year, while continuing MTX. Patients who had completed the 52-week trial were subsequently eligible for an open-label extension, during which all patients received adalimumab 40 mg qwq plus MTX. At 52 weeks ACR20/50/70 response rates in the 40 mg qwq group were 58.9%, 41.5% and 23.2% respectively, whereas the respective rates for the placebo group were 24%, 9.5% and 4.5%. For those who completed 5 years of treatment with adalimumab ACR20/50/70, response rates further improved, being 75%, 58% and 35% respectively.

In the PREMIER study, 799 MTX naïve patients with early RA were randomized to either adalimumab 40mg sc qow or MTX 7.5 to 20 mg weekly or a combination of both and were followed for up to 2 years with ACR50 response being a co-primary end-point. ACR50 response rates achieved at the end of year 1 were maintained till the end of year 2 (ACR50 rates at year 1 were 41%, 46%, 62% for the adalimumab, MTX and the combination group and ACR50 rates at year 2 were 37%, 43%, 59% respectively). Similar sustained efficacy was observed for ACR20, ACR70 and ACR90 scores. Clinical remission at year 1 was achieved by 43% of patients receiving combination therapy, 23% of patients receiving adalimumab monotherapy and 21% of patients receiving MTX monotherapy. The respective rates at year 2 were 49%, 25% and 25%. Following a 3-year open-label extension, during which all enrolled patients received adalimumab with or without MTX, DAS28<2.6 was achieved by 67%, 54% and 52% of patients initially randomized to combination, adalimumab and MTX mono-therapy groups.

ReAct was a 12-week multinational open-label study of patients with active established RA and previous failure of classic DMARDs or even TNFα blockers with an optional extension phase. In this study adalimumab was proven effective and safe for both the treatment of patients with prior discontinuation of infliximab and/or etanercept (due to inadequate response, loss of response or intolerance), as well as of TNFα blocker naïve patients. Patients who had been for ≤1 year in ReAct were allowed to participate in ReAlise, a study evaluating the long-term efficacy and safety of adalimumab. Results are currently available for the first 3 years of the trial. Among 658 patients who have completed 3 years in ReAlise, ACR20/50/70 response rates were 85%, 65% and 40%, which are at least comparable to the respective baseline (at ReAlise initiation) values of 80%, 59% and 35%.

In a long-term open-label study of patients previously included in various adalimumab trials, the efficacy of the combination of adalimumab plus MTX was assessed for up to 7 years. In this study the improvement in the various disease activity measures achieved during the first year of therapy was sustained (Health Assessment Questionnaire- HAQ) or even improved (ACR response rates, DAS28, joint counts, clinical remission rates) during the subsequent observation period.
Long-term inhibition of radiographic progression was initially assessed in a 2-year follow-up of a phase I study in which 47 patients with established RA were given adalimumab monotherapy. Hand and feet radiographs at baseline, year 1 and 2 were available for 36 patients. Patients with stable radiographic course were more often ongoing adalimumab recipients, while patients with radiographic deterioration were more likely to have stopped adalimumab.

Radiographic efficacy at 1 and 2 years was also a co-primary endpoint in the PREMIER study. Increases in the modified total Sharp score (mTSS) were significantly less in the adalimumab plus MTX group compared to the adalimumab monotherapy and MTX monotherapy groups both at year 1 and 2. Interestingly, even if the ACR response rates were comparable between the adalimumab and MTX monotherapy groups, the adalimumab monotherapy group had less radiographic progression at all time points than the MTX monotherapy group. There seemed to be a decrease in the radiographic progression rate during year 2 as compared to year 1 in the patients treated with the combination, while the rate remained stable in the MTX monotherapy group.

In a subanalysis of the PREMIER study, combination recipients were also shown to have less hand bone loss as measured with digital X-ray radiogrammetry at year 1 and 2 years.

After 3 years of open-label treatment, during which all enrolled patients received standard dose of adalimumab with or without MTX, patients initially randomized to adalimumab plus MTX group had less radiographic progression from baseline than patients initially randomized to adalimumab or MTX monotherapy groups (mTSS change from baseline 2.8, 7.4, 9.2 for the three groups respectively). After 5 years, no radiographic progression was observed in half of patients initially randomized to the combination therapy, compared to one third of patients in the initial monotherapy groups. Moreover, between years 2 and 5 less radiographic progression was observed in patients initially randomized to either adalimumab group than to MTX monotherapy group.

Likewise, a 5-year follow-up of patients with established RA who had initially participated in the DE019 study yielded similar results. During the one-year double-blind phase patients allocated to the placebo-plus-MTX group had a mean...
mTSS change of 2.51. For patients receiving adalimumab 40 mg qow plus MTX the 1-year value was −0.62 and after 5 years of adalimumab exposure the mean mTSS change had slightly increased to 0.83. By year 5, 58% of the patients initially treated with adalimumab 40 mg qow had no further radiographic progression, but for the initially placebo-treated patients the corresponding value was 40%.87

Moreover, in an uncontrolled study of adalimumab efficacy as assessed both clinically and in terms of musculoskeletal ultrasound (US) in patients with established RA taking concomitant DMARDs, the improvement in clinical disease activity as well as in the US scores achieved at 3 months was maintained for the whole 24-month observation period.88 Similarly, in a 1-year follow-up study of patients with refractory RA, treatment with adalimumab resulted in clinical and laboratory improvement, as well as decrease of the volume of the active inflammatory tissue as assessed with magnetic resonance imaging of the hands before and 1 year after treatment.89 Furthermore, in patients who had previously failed infliximab (due to lack or loss of response or intolerance), adalimumab produced significant responses which were sustained for up to 56 weeks (ACR20 at 56 weeks 43%–65% depending on reason for infliximab discontinuation),90 consistent with our own findings.91 Better responses were observed among those who had lost of infliximab efficacy and poorer responses among those who had had primary lack of efficacy. The presence of human anti-chimeric antibodies (HACA) did not seem to substantially affect adalimumab efficacy after infliximab failure.92

As regards comparison between adalimumab with infliximab and etanercept, an indirect comparison between the three agents was attempted in the context of a meta-analysis of 3 randomized controlled trials (duration up to 54 weeks) of the three drugs in established RA. The results implied that adalimumab was more efficacious compared to etanercept, but comparable to infliximab in terms of ACR20/50/70 responses. Conversely, etanercept was associated with fewer withdrawals due to adverse events compared to adalimumab.93 However, an earlier meta-analysis of 4 randomized trials of the three drugs and their adjusted indirect comparison failed to show differences in ACR 20 and 50 responses among the three agents.94 Moreover, in a retrospective study of RA patients treated with TNFα blockers, infliximab continuation rates over 2 years were significantly lower than etanercept and adalimumab. The main reason for infliximab withdrawal was loss of efficacy, whereas for etanercept it was adverse events and for adalimumab lack of response.95 In another retrospective study of patients with RA, AS and PsA, discontinuation rates were similar across the three drugs over 2 years; a trend for better tolerance of adalimumab and etanercept comparing to infliximab was noted though.96 Finally, in the Swiss registry of anti-TNF therapies in RA, patients receiving infliximab were more likely to have their DMARD treatment intensified than those treated with etanercept or adalimumab. Furthermore, infliximab recipients were more likely to have their infliximab dose gradually increased, although one has to consider that the pharmacotechnical form of infliximab allows for more flexible dose adjustments. Discontinuation rates were similar among the three drugs.97

Ankylosing spondylitis
Multiple randomized placebo-controlled trials have been conducted to evaluate the clinical and radiographic efficacy and safety of adalimumab in patients with AS after failure of conventional non-steroidal anti-inflammatory drugs (NSAIDs) and/or DMARDs,34,105 in patients with pre-radiographic spondyloarthropathy,106 as well as in patients with total spinal ankylosis.107 The results of the above-mentioned studies that involved no more than 52 weeks of observation were consistent with a considerable efficacy of adalimumab compared to placebo and an acceptable safety profile. Furthermore, both a retrospective and a prospective (20 weeks long) observational study reported beneficial effects of adalimumab as regards flares of anterior uveitis in patients with active AS.108–109

Long-term efficacy of adalimumab in AS is assessed in a 5-year open-label extension of the ATLAS study,34 in which after completion of the initial 24-week, double-blind, placebo-controlled phase of the trial, all enrolled patients received 40 mg adalimumab qow. Data currently exist for the first 3 years of observation. Briefly, after 24 weeks of adalimumab exposure 20% improvement according to the Assessment of Spondyloarthritis International Society criteria (ASAS20), ASAS40, ASAS5/6 and ASAS partial remission responses were achieved by 65.2%, 46.1%, 58.6% and 24.2% of the patients respectively. At 2 years the respective percentages were 64.5%, 50.6%, 58.9% and 33.5% (last observation carried forward [LOCF] analysis). Similar sustained efficacy was evident for the individual components of the ASAS20 score [patient’s global assessment of disease activity during the previous week, total back pain during the previous week, Bath Ankylosing Spondylitis Functional Index (BASFI) score and inflammation, represented by the mean of the severity and duration of morning stiffness], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),
CRP and the enthesitis score. Clinical efficacy was maintained also during the third year of observation. As regards metrology, adalimumab-treated patients achieved better outcomes concerning lumbar side flexion, cervical rotation, and intermalleolar distance which were sustained over 3 years.

An analysis of the subgroup of the ATLAS population with total spinal ankylosis was also reported separately from the main study results. In this patient group, at 12 weeks adalimumab produced ASAS20, ASAS40, ASAS5/6 and BASDAI50 responses in 50%, 33%, 33% and 33% respectively of patients receiving the active drug, but in no patient receiving placebo. Response rates were sustained for up to 2 years of treatment, although ASAS partial remission was rare due to failure of the patients with total spinal ankylosis to report a BASFI score less than 2.

In the extension of ATLAS, spine radiographic outcomes after 2 years of adalimumab therapy were compared with respective radiographic data from a historical cohort of AS patients who were anti-TNFα naïve. No difference in radiographic progression was observed between the 2 groups of patients, despite the clinical improvement of the adalimumab-treated patients.

**Psoriatic arthritis**

Adalimumab has been assessed compared to placebo in 2 randomized double-blind trials: a 24-week study involving 313 patients with active PsA refractory to NSAIDs, followed by an open-label active treatment phase; and a 12-week study involving 100 patients with active PsA refractory to DMARDs, followed by an open-label extension phase as well. MTX use was allowed in both studies provided that the dosage was stable prior to study entry. In the ADEPT trial, 296 patients either initially allocated to adalimumab or switched from placebo after the double-blind phase were followed for up to additional 120 weeks. Clinical responses to adalimumab achieved at 48 weeks were maintained for up to 104 weeks: at 48 weeks ACR20/50/70 responses were 58.7%, 42.7% and 27.8% respectively, whereas at 104 weeks the respective values were 57.3, 45.2% and 29.9%. Response rates according to the PsA Response Criteria (PsARC) at 48 weeks were 65.9% and remained 63.5% at 104 weeks. Skin involvement improved from baseline to 48 weeks and this improvement was sustained for up to 104 weeks. The percentage of patients classified as “clear” or “almost clear” according to physician’s assessment increased from 6.2% at baseline to 63.6% at 48 weeks and subsequently remained almost stable by 104 weeks (56.6%). The Psoriasis Area and Severity Index 50% response rates (PASI50), PASI75, PASI90 and PASI100 responded in a similar fashion, with PASI100 achieved by >20% of patients between weeks 48 and 104. Enthesitis and dactylitis indices decreased from baseline to week 24 (though not significantly) and were equally suppressed up to 104 weeks. Radiographic progression as assessed with the mTSS slowed during the initial double blind phase of the study in the adalimumab group, while it kept on progressing in the placebo group (the mean mTSS change from baseline to 24 weeks was −0.2 for the adalimumab group and 1.0 for the placebo group). Among the initially adalimumab-treated patients no radiographic progression between baseline and week 24 was observed in 89.6% and between week 24 and week 144 in 77.4% of patients. For initially placebo-treated patients no radiographic progression was observed in 70.3% between baseline and

**Table 2** Summary of studies with long-term extensions of adalimumab in ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA)

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants initially enrolled</th>
<th>Study protocol</th>
<th>Original study duration</th>
<th>Maximum follow-up</th>
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<tr>
<td>ATLAS</td>
<td>315 pts with active AS</td>
<td>Ada 40 mg qow OR placebo</td>
<td>24 weeks</td>
<td>3 years</td>
<td>227</td>
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<tr>
<td>ADEPT</td>
<td>313 pts with active PsA</td>
<td>Ada 40 mg qow OR placebo</td>
<td>24 weeks</td>
<td>2 years</td>
<td>298</td>
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<tr>
<td>Lovell</td>
<td>171 pts with JIA</td>
<td>Ada 24 mg/m² BSA with or without MTX</td>
<td>16 week open-label lead-in phase, followed by a 32-week double blind phase</td>
<td>3 years</td>
<td>NP</td>
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**Abbreviations:** Pts, patients; MTX, methotrexate; Ada, adalimumab; qow, every other week; BSA, body surface area; NP, not provided.
week 24, but it rose to 77.3% between weeks 24 and 144, that is to levels similar to the initially adalimumab-treated patients for the same study period. Finally, a meta-analysis of randomized trials of the 3 TNFα blockers for the treatment of PsA, showed no significant differences among the 3 drugs over 24 weeks in terms of efficacy (ACR50).116

Remarkably, whereas all 3 TNFα blockers are licensed for treatment of PsA and psoriasis, there have been a number of cases reported of psoriasis induction in patients treated with these drugs for a variety of conditions. According to a recent review, 19 cases of psoriasis have been reported in adalimumab recipients for RA and 1 for AS.117

**Juvenile idiopathic arthritis**

To date a single 32-week, double-blind, placebo-controlled study with a preceding 16-week open-label lead-in phase has recently been published concerning the use of adalimumab in children with JIA. In the initial 16-week open-label phase, ACR Pediatric 30% (ACR Pedi 30) response rates, as well as ACR Pedi 50/70/90 rates were 74%, 64%, 46% and 26% in the adalimumab monotherapy group and 94%, 91%, 71% and 28% in the adalimumab plus MTX combination group respectively.118 After the initial 48 weeks of the trial, 128 patients were enrolled in a 2-year open-label extension by the end of which clinical response was shown to be sustained: ACR Pedi 30/50/70/90 response rates were 89%, 86%, 77% and 59% respectively with 40% of patients having achieved an ACR Pedi 100 response.119

**Safety**

The safety profile of adalimumab in its various indications has been evaluated in several controlled clinical trials and their open-label extensions, in observational studies, through spontaneous reports of adverse events and through biologic drug registries, after the drug had been released in the market. During the short time frame of the placebo-controlled clinical trials in RA, AS, PsA and JIA, rates of adverse events in the adalimumab-receiving groups, in most cases, were comparable to the rates observed in the placebo groups.7,34,81–84,106,113,114,118

Adverse events were reported more often in the adalimumab group in the ATLAS34 study. In the study by Keystone et al rates of serious infections were higher in the adalimumab 40 gow group compared to placebo group, although this was not confirmed for the adalimumab 20 mg weekly group.84 In the PREMIER study, serious infections were more frequent with the combination therapy, while they occurred at similar rates in the two monotherapy groups.7 In the study by Haibel et al respiratory and skin infections occurred in more adalimumab than placebo-treated patients.106 Apart from injection site reactions (pain, erythema, localized rash, hemorrhage), which were usually more frequent compared to placebo,34,81,83 the most common adverse reactions to adalimumab across the studies were upper respiratory tract infections, rhinitis, sinusitis, rash (at sites remote to the injection ones), headache and pruritus. Although adalimumab is not expected to relate to allergic reactions, owing to its fully-human sequences, we have reported a case of acute systemic aphylactic reaction with urticaria, angioedema and hypotension at the seventh injection of the drug.120

Long-term safety data of adalimumab across several studies are summarized in Table 3. Throughout the 4-year extension of the ARMADA trial serious adverse events were similar to those observed during the initial double-blind phase. The incidence of serious infections was 2.03/100 patient-years (PY) compared to 2.3/100 PY in the initial phase and corresponded to cases of pneumonia, urinary tract infections and septic arthritis. No cases of tuberculosis or other opportunistic infections were observed. Among 19 cancers observed there were 2 cases of leukemia (acute myeloid and chronic lymphocytic respectively) resulting in an incidence rate of 0.23/100 PY, but no cases of lymphoma. Five cases of basal skin cancer and one case of melanoma were also observed. One patient developed multiple sclerosis and another one congestive heart failure (CHF) with an incidence rate 0.11/100 PY for each. No cases of lupus-like syndrome or unusual adverse reactions were observed.86

In ReAlise, during 7032 PY of adalimumab exposure the rates (per 100 PY) of serious infections and of tuberculosis were 2.57 and 0.16 respectively.91 The rate of malignancies was 1.17/100 PY, while the standardized incidence rates (SIR) compared to the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database was 0.89 (95% confidence interval [CI] 0.68–1.13) for all cancers and 3.81 (95% CI 1.9–6.81) for lymphomas.91 In a 7-year open-label study of RA patients previously included in adalimumab trials, 58% of patients continued treatment with adalimumab plus MTX into the 7th year. Types and rates of serious adverse events were consistent with those in randomized control trials, while exposure-adjusted serious adverse event and serious infection rates seemed to decline over time.92

Prior to the publication of the above-mentioned extension studies, a concise report about safety of adalimumab in patients with RA had shown that long-term adalimumab treatment is generally well tolerated and the drug presents a safety profile similar to the other TNFα blockers. Among
a total of 10050 patients treated for 12506 PY, more than 300 of them having been exposed to adalimumab for over 5 years, the rate of serious infections was 5.1/100 PY which was similar to serious infections rates of the RA patients in general. After implementation of pre-treatment screening and prophylactic therapy, tuberculosis rates in Europe declined from 1.3/100 PY to 0.33/100 PY, while the rate in North America was lower (0.08/100 PY).121 After 12506 PY of RA patients exposure the rates of lymphoma were 0.12/100 PY. Various types of lymphomas have been observed including Hodgkin’s disease, T and B cell lymphoma and mucosa-associated lymphoid tissue lymphomas. The SIR of lymphoma, when adalimumab-treated RA patients were compared to the general population in the SEER database was 3.19, which was deemed consistent with the SIR for RA patients not treated with TNFα blockers.121 After 12506 PY of RA patients exposure to adalimumab 10 cases of demyelinating disorders have been observed, including multiple sclerosis and Guillain-Barré syndrome, with an incidence for the whole group of disorders approximately 0.08/100 PY. Systemic lupus erythematosus and related conditions have been observed in 13 cases, resulting in an incidence rate of 0.1/100 PY.121

In a meta-analysis of randomized controlled trials of infliximab and adalimumab in RA (with a duration of 12 to 54 weeks) it was shown that the use of both drugs was associated with an increased risk of serious infections and malignancies, although this meta-analysis has been criticized for using incidence rates rather than exposure-adjusted measures (like PY) for the calculations.122

The rates and type of adverse events of adalimumab during the extension of the ATLAS trial were consistent with those observed during the initial double-blind period. The incidence rates (per 100 PY) in the extension phase as opposed to the initial phase were respectively 10.5 and 10.2 for serious adverse events and 1.1 and 0.0 for serious infections. Four cases of oral candidiasis (incidence rate 0.7/100 PY) were observed, but no cases of tuberculosis, demyelinating disorder, lupus-like syndrome or CHF. Among 4 cases with cancer there was 1 case of Hodgkin’s disease that regressed after adalimumab was discontinued without further treatment and 2 cases of non-melanotic skin cancer and a case of melanoma.11

Similarly, the safety profile of adalimumab during the extension phase of the ADEPT trial was comparable to the initial phase of the trial. The incidence rates (per 100 PY) in the extension phase as opposed to the initial phase were respectively 9.2 and 7.5 for serious adverse events and 2.4 and 0.7 for serious infections. Four cases of oral candidiasis (incidence rate 0.6/100 PY) were observed and 1 case of peritoneal tuberculosis (incidence rate 0.1/100 PY), but no cases of a demyelinating disorder, lupus-like syndrome or CHF. Among 4 cases with cancer there was 1 case of lymphoma and 2 cases of non-melanotic skin cancer.11 Finally, long-term use of adalimumab in patients with JIA was not associated with increased risks comparing to short-term safety as assessed in a clinical trial.119

Assessment of the safety of adalimumab in global clinical trials across all its indications showed that over 10 years of clinical trial experience its safety profile has remained stable. Adalimumab safety in AS, PsA, JIA, psoriasis and Crohn’s disease is consistent, if no better than in RA. Serious infection rates (per 100 PY) were 4.65, 2.81, 1.11 and 2.76 for RA, PsA, AS and JIA respectively, pneumonia being the most common type of infection in RA patients. The SIR of malignancies for all 6 diseases combined was 0.83 (95% CI 0.72–0.96). As regards lymphomas, their incidence was 0.12, 0.2, 0.08 and 0.0 per 100 PY for RA, PsA, AS and JIA respectively, with their incidence being statistically greater than expected only in RA patients (SIR 2.98, 95% CI 1.89–4.47). The standardized mortality ratios (SMR) of adalimumab recipients calculated using the World Health Organization mortality data were less than 1 for RA and for PsA, while no deaths were observed in AS and JIA trials.121

The issues of tuberculosis and cancer may better be addressed by long-term follow-up of anti-TNFα-treated patients through registries. Indeed, in the British biologics registry RA patients treated with TNFα blockers were no more likely to suffer a serious infection than DMARD-treated RA patients. However, anti-TNFα use was associated with an increased risk for skin and soft tissue infections, as well as infections due to intracellular pathogens, including tuberculosis. The rates of serious infections were similar among the 3 TNFα blockers.124 In a more recent report on the British registry, the adjusted incidence rate ratio (AIRR) (95% CI) of serious infections for patients on TNFα blockers compared to DMARD-only receiving patients was 1.22 (0.88–1.69) collectively for all 3 agents, with each individual agent’s CI crossing unity. However during the first 3 months of treatment, the risk of serious infection in TNFα blocker recipients was significantly higher than in DMARD-only recipients (AIRR 4.1 for etanercept, 5.6 for infliximab, 3.9 for adalimumab, all significant).125 In an Italian registry of RA patients on anti-TNFα agents, the incident of severe infections was 3.58/100 PY. They consisted mostly of lower respiratory tract, skin
Table 3 Summary of adverse events across various long-term adalimumab studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>PY of exposure</th>
<th>AE</th>
<th>SAE</th>
<th>Serious Infections</th>
<th>TB</th>
<th>Cancer</th>
<th>Demyelination</th>
<th>Lupus-like syndrome</th>
<th>CHF</th>
<th>Deaths</th>
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<tr>
<td>ARMADA extension&lt;sup&gt;86&lt;/sup&gt;</td>
<td>RA</td>
<td>886</td>
<td>NP</td>
<td>3.15</td>
<td>2.03</td>
<td>0</td>
<td>2.14</td>
<td>0.11</td>
<td>0</td>
<td>0.11</td>
<td>0.7</td>
</tr>
<tr>
<td>ReAlise&lt;sup&gt;91&lt;/sup&gt;</td>
<td>RA</td>
<td>7032</td>
<td>NP</td>
<td>2.57</td>
<td>0.16</td>
<td>1.17</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>0.7</td>
</tr>
<tr>
<td>Weinblatt&lt;sup&gt;92&lt;/sup&gt;</td>
<td>RA</td>
<td>5720</td>
<td>NP</td>
<td>3.2</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Schiff MH&lt;sup&gt;121&lt;/sup&gt;</td>
<td>RA</td>
<td>12506</td>
<td>NP</td>
<td>5.1</td>
<td>0.27</td>
<td>Lymphoma: 0.12</td>
<td>0.08</td>
<td>0.1</td>
<td>0.28</td>
<td>NP</td>
<td></td>
</tr>
<tr>
<td>ATLAS extension&lt;sup&gt;91&lt;/sup&gt;</td>
<td>AS</td>
<td>533.7</td>
<td>445.6</td>
<td>10.5</td>
<td>1.1</td>
<td>0</td>
<td>0.7</td>
<td>0</td>
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<tr>
<td>ADEPT extension&lt;sup&gt;115&lt;/sup&gt;</td>
<td>PsA</td>
<td>676.5</td>
<td>292.2</td>
<td>9.2</td>
<td>2.4</td>
<td>0.1</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Lovell&lt;sup&gt;119&lt;/sup&gt;</td>
<td>JIA</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NP</td>
</tr>
<tr>
<td>Burmester&lt;sup&gt;123&lt;/sup&gt;</td>
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<td>1255.2</td>
<td>NP</td>
<td>1.11</td>
<td>0</td>
<td>0.16&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.08</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>JIA</td>
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<td>NP</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NP</td>
</tr>
</tbody>
</table>

<sup>*</sup>Excluding non-melanoma skin cancer.

**Abbreviations:** AE, adverse events; SAE, serious adverse events; TB, tuberculosis; CHF, congestive heart failure; NP, not provided; RA, rheumatoid arthritis; PsA, psoriatic arthritis; JIA, juvenile idiopathic arthritis; AS, ankylosing spondylitis.
and soft tissue infections, while 4 were fatal. There was no statistically significant difference in the occurrence of severe infections between different TNFα blockers in this database.126 In the Spanish registry of biologic treatments for rheumatic diseases the incidence of tuberculosis for all 3 TNFα inhibitors before and after the dissemination of recommendations for tuberculosis prophylaxis was 0.47/100 PY and 0.17/100 PY respectively. After all 3 TNFα blockers were fully available no statistical difference in the tuberculosis incidence between the three drugs was observed.48

In the Swedish registry, RA patients treated with TNFα blockers had a statistically increased relative risk (RR) for malignant lymphoma compared to the general population (RR 2.72, 95% CI 1.82–4.08), but not compared to anti-TNFα-naïve RA patients (RR 1.35, 95% CI 0.82–2.11). However, none of the 3 TNFα blockers was associated with a statistically different risk for lymphoma development compared to the other two.127

Finally, a French case-control study assessing the risk of lymphoma among patients treated with various TNFα blockers according to drug type and in comparison with the general population showed an increased risk of lymphoma among monoclonal antibody recipients as opposed to TNF receptor construct recipients.128

Patient-focused outcomes

Apart from measures of disease activity and radiographic progression, several patient-reported outcomes (PRO) relating to the impact of disease and its treatment on various aspects of patients’ lives have been assessed during the long-term use of adalimumab for inflammatory arthritides. In the ARMADA trial the Disability Index of the Health Assessment Questionnaire (HAQ DI) decreased from an initial 1.52 to 1.55 by 0.54 to 0.62 during 6 months. This decrease was sustained in the following 4-year open-label extension by 0.54 to 0.62 during 6 months. This decrease was sustained in the following 4-year open-label extension with a HAQ DI score equal to 0.8 at years 1 through 3 and 0.7 at year 4.46 Mittendorf et al in an open-label study followed up for 3 years patients with established RA who had previously participated in adalimumab clinical trials and assessed the following health-related quality-of-life (HRQoL) measures before adalimumab treatment, at 26 weeks and at 170 weeks: Medical Outcomes Study Short Form-36 Health Survey (SF-36) covering 8 domains of health status (physical functioning, bodily pain, role-physical, role-emotional, general health, mental health, vitality, social functioning) with scores between 0 (worst) and 100 (best); Functional Assessment of Chronic Illness Therapy-Fatigue scale (FACIT-Fatigue), a measure of oppressive fatigue experienced by the patient with a score between 0 (worst) and 52 (best); and the Health Utilities Index Mark 3 (HUI3), a measure of health-related utility of patients with a score of 0 equal to death, 1.0 implying perfect health and negative scores implying health states considered worse than death. Adalimumab was shown to generate statistically significant and clinically meaningful improvements in all of the above HRQoL measures shortly after the beginning of the treatment which were sustained for up to 3 years.129 The same group of investigators conducted a survey on the same patient population regarding various other patient-focused outcomes: pain (expressed through a visual analogue scale, VAS), morning stiffness duration, disease-related expenditures (need for personal help, transportation, aids and devices) either offered free of charge or paid by the patient or a third party, and the impact of disease on productivity at work or at the household. Pain showed a rapid and sustained improvement and morning stiffness kept on decreasing during the 144-week follow-up period. For the rest of the outcomes, no deterioration was observed during the follow-up period of this patient population with established RA.130 For the specific impact of adalimumab treatment on work participation, occupational data from the aforementioned RA population were compared to those of DMARD-treated patients enrolled in a Norwegian registry. During the 2 years of observation patients treated with adalimumab were more often working and worked for more time than DMARD-treated patients. The hazard ratio for stopping work was smaller for adalimumab-treated patients and independent of clinical status achieved.131

In the early RA patients evaluated in the PREMIER study, adalimumab plus MTX combination therapy produced greater improvements in HAQ DI scores at year 1 than adalimumab or MTX monotherapy groups. At year 2, the combination therapy group showed a greater HAQ DI reduction compared to the MTX monotherapy group, but not to adalimumab monotherapy group.7 In a subanalysis of the PREMIER study comparing the SF-36 responses in the MTX plus adalimumab combination group and the MTX monotherapy group to SF-36 scores of the United States population, it was shown that both combination therapy and MTX monotherapy effectively increased vitality, mental health and social function scores, but combination therapy was more effective in increasing bodily pain and global health scores and the Physical Component Summary (PCS) score than MTX monotherapy during the 2 years of the trial. Better PCS scores, as achieved...
Long-term PRO with the use of adalimumab in AS derive from an open-label extension of the ATLAS trial. Ankylosing Spondylitis Quality of Life Questionnaire (ASQOL), SF-36 PCS score and SF-36 Mental Component Summary (MCS) score were evaluated at 24 weeks and then throughout 2 years. Using LOCF analysis, a baseline ASQOL score of 10.2 to 10.6 decreased to 6.3 after 24 weeks, 6.1 after 1 year and 5.8 after 2 years. Similarly SF-36 PCS score increased from a baseline value of 31.8 to 32.9, to 40.2 after 24 weeks, 41.5 after 1 year and 41.9 after 2 years. Both PCS and MCS score increases over 2 years exceeded the minimum clinically important difference, the MCS score responding less than the PCS score.

Finally, for PsA, long-term PRO are described in the open-label extension of the ADEPT study. Patients receiving adalimumab reported a mean 0.3 decrease of the HAQ DI already at 24 weeks, which was sustained for up to 104 weeks. Furthermore, during the initial 24-week of the trial, the PCS score of the SF-36, the Dermatology Life Quality Index (DLQI), the FACIT-F and the patient’s global assessment of pain and disease activity showed a significant and clinically meaningful improvement in the active treatment group compared to placebo. At the open-label extension the changes of the above indices from baseline through 104 weeks of adalimumab exposure were similar to changes observed already in the first 24 weeks. In particular HAD DI score decreased by 0.3 from baseline through 104 weeks, SF-36 PCS score increased by approximately 9.4, SF-36 MCS increased slightly by 2.3 (not clinically meaningful), FACIT-F increased by 6.1, DLQI fell by 5.8, VAS-pain declined by 23.4 and patient’s global assessment of disease activity decreased by 21.6.

**Expert opinion**

Adalimumab, a fully humanized monoclonal antibody against TNFα, presents an attractive option for the treatment of patients with chronic inflammatory arthritides. Even if head-to-head trials comparing adalimumab with infliximab and etanercept are yet not available, adalimumab seems as effective as the other TNFα blockers.

In RA, the once-unattainable goal of remission can now be achieved with adalimumab which can produce disease remission in 23% to 43% of patients within 1 year of therapy, while its efficacy is maintained or even enhanced in the subsequent years with the rates of patients achieving remission reaching even 67%. Apart from suppressing inflammation, adalimumab might be regarded as having disease-modifying properties, granted that early treatment with adalimumab seems to protect from structural damage in the long term more effectively than delayed treatment, while this effect seems independent of the degree of suppression of the inflammation. The sustained effectiveness of adalimumab in both disease activity and radiographic progression is obviously reflected in the quality of patients' lives and is evidenced in the various PRO measures. Moreover, it should be noted that adalimumab is not effective only when prescribed to patients with a poor response or intolerance to classic DMARDs; it is also effective and well tolerated by patients who have previously shown lack or loss of response or even intolerance to other TNFα antagonists. Thus, adalimumab may be considered as an alternative or even the third TNFα blocker for the treatment of patients who have already failed infliximab, etanercept or both.

Although fewer patients with AS, PsA and JIA have been treated with adalimumab within clinical trials and observational studies compared to RA, the available evidence points to a substantial benefit of adalimumab both in clinical grounds and in PRO, which is maintained during long-term treatment. Thus, adalimumab is a promising therapeutic choice for the treatment of patients with these diseases who have failed conventional therapeutic modalities. In particular, axial involvement in spondyloarthropathies allows for a single treatment option after NSAIDs have failed: TNFα blockers. Indeed treatment of AS with adalimumab has resulted in a great and durable improvement of disease activity and functionality, benefiting even patients with total spinal ankylosis. Although adalimumab has not been shown to halt axial radiological progression over 2 years, neither infliximab nor etanercept have done so in the same time frame. Perhaps, longer treatment durations might be needed, until an inhibiting effect on the reparative bone formation (syndesmophytes) can be observed. Alternatively, early treatment of axial involvement, before erosions have already taken place, might prevent ankylosis.

After almost 10 years of use of adalimumab in patients with rheumatic diseases no new safety signals have emerged. Tuberculosis reactivation is a class effect pertaining to the whole group of TNFα blockers. Screening for tuberculosis and preventive therapy of patients exposed to the mycobacterium is thus mandatory when prescribing adalimumab. Moreover, constant vigilance is required for early diagnosis and appropriate treatment of tuberculosis or other opportunistic infections in patients on TNFα blockers. Malignancies have been a major source of concern with...
the focus on hematological malignancies, especially in RA patients. Even if TNFα blocker recipients are at a greater risk for lymphoma, it has not yet been proven beyond doubt that the extra risk these patients are subject to derives from the drug exposure, from the severity of their RA or both. Until more data on patients exposed to adalimumab as well as other immunosuppressive drugs are available, rheumatologists should be vigilant for the emergence of such a complication.

Conclusion
In conclusion, adalimumab is an effective drug with an acceptable safety profile for adults with RA, AS and PsA, as well as children with JIA. Its effectiveness is obvious not only across the various clinical and laboratory measures of disease activity, but also on the patients’ quality of life and functionality indices. Furthermore, its effectiveness and safety profile seem to be maintained for years during continuous adalimumab therapy.

Disclosures
The authors declare no conflicts of interest.

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