Chapter 4

Cytokine inhibitors

Tumor necrosis factor inhibitors

Importance of tumor necrosis factor in joint inflammation

Tumor necrosis factor (TNF; formerly designated TNF-α) is a cytokine of central importance in multiple inflammatory processes. Its initial discovery was in the field of oncological research, where in the early 1980s it was established as the mediator of tumor-related cachexia (and because of this it was also named 'cachectin') and in separate lines of research it was shown to be capable of inducing necrosis of malignant cells in vitro, giving it its current name. While its role in tumor surveillance and anti-tumor immunity remains of interest – and TNF is in fact approved as a treatment for certain sarcomas – the role of TNF in immunity attracted increasing interest and led to dramatic therapeutic developments. In the mid-1980s, studies by Firestein, Zvaifler, and others established that TNF and interleukin (IL)-1 were among the most dominant cytokines in the inflamed synovium of RA patients [1,2]. Feldmann and others established TNF as a key cytokine in the cellular inflammatory process in autoimmune thyroiditis [3]. Subsequent studies of the inflamed rheumatoid synovium revealed a similar major presence for this cytokine [4]. In an important experiment, Brennan et al [5] demonstrated that blocking TNF in vitro in synovial explant cultures from patients with rheumatoid arthritis (RA) would downregulate not only TNF but also IL-1, while blocking IL-1 did not abrogate the excessive production of TNF (Figure 4.1).

These findings supported the first use of anti-TNF therapies in RA. Further work has attempted to characterize the role of TNF in rheumatoid

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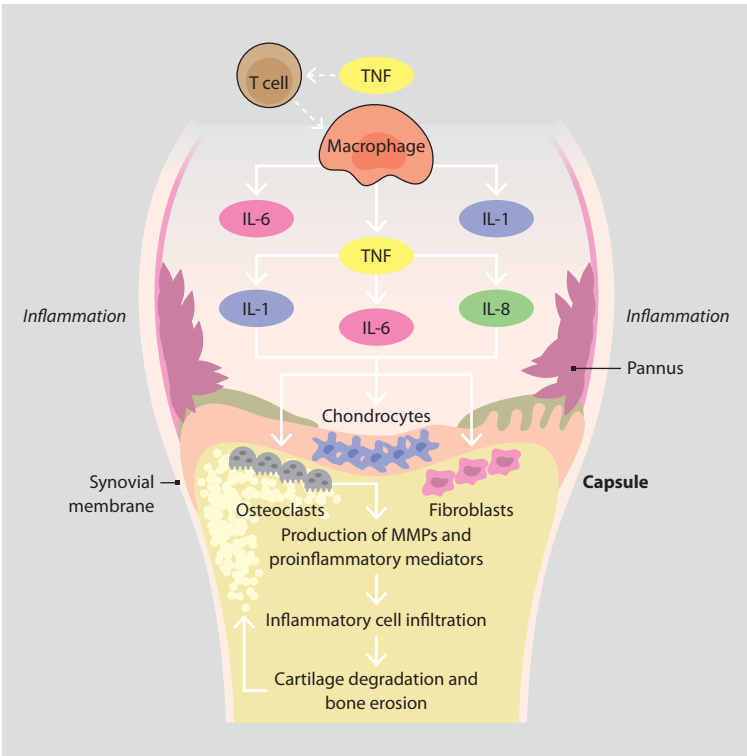

Figure 4.1 The pathophysiology of rheumatoid arthritis depicted as a cascade, in which tumor necrosis factor (TNF) is upstream from interleukin (IL)-1, IL-6, and IL-8. MMP, matrix metalloproteinases.

inflammation in more detail. Some hypothesized that TNF was an 'upstream' cytokine, directing inflammation through a sequence of events where IL-1, IL-6, and other cytokines were more 'downstream' [6]. However, experimental data did not clearly support such a view and many experts today consider the active inflammation in the synovium in established RA to be the result of multiple cascades of inflammatory pathways running in parallel with extensive cross-talk and with no clear single orchestrator molecule. Nevertheless, the therapeutic success of TNF blockade makes it abundantly clear that TNF plays an important, if not completely central, role in RA and other types of inflammatory arthritis and synovitis.

Overview of tumor necrosis factor inhibitor therapy

To date, five unique anti-TNF agents have been clinically developed, approved, and are used in rheumatology practice; a biosimilar anti-TNF has received regulatory approval in Europe and is already being used in some countries; and several other biosimilars for existing anti-TNF agents are under clinical development. Remarkably, only one anti-TNF agent, lenercept, failed in clinical development to date [7]. Anti-TNF therapies revolutionized therapeutics for RA and other inflammatory musculoskeletal diseases by offering unparalleled efficacy and favorable safety profiles. They also generated new safety concerns (for example, reactivation of latent tuberculosis) and spawned the development or strengthening of entirely new directions in clinical rheumatology research including long-term surveillance and health economics. Last but not least, the anti-TNF biologics, and biologics in general, completely changed the economic perspectives in rheumatology. From a discipline where drug costs were almost negligible rheumatology has now become the specialty associated with some of the highest drug costs worldwide. In 2013, three anti-TNF agents were in the top ten of highest-grossing medications in the United States, accounting for around $14 billion in sales.

Currently available tumor necrosis factor inhibitor therapies

Adalimumab

Adalimumab (Humira) was originally developed in the 1990s at the German pharmaceutical company Knoll with the designation D2E7. Whereas most therapeutic monoclonal antibodies had originally been generated in mice and subsequently grafted onto a human immunoglobulin framework, resulting in a chimeric monoclonal antibody molecule, D2E7 was the result of a novel process based on recombinant DNA technology where human genes coding for antibody chains were generated through phage-display, selected, and recombined so as to achieve specific TNF-binding while remaining fully human. Once established, the monoclonal was propagated in Chinese hamster ovary (CHO) cells, as is the case for most biologics. It was anticipated that the fully human structure might convey certain benefits, particularly with respect to immunogenicity.

The initial development of D2E7 was as an intravenous compound, and early trials in patients with RA revealed good efficacy [8]. However, a distinct safety concern was also identified: in these early trials performed in Germany a small number of patients developed clinically manifest tuberculosis, most likely due to reactivation of latent tuberculosis. In hindsight this was the first warning of more significant developments several years later.

Development of D2E7 was continued as a subcutaneous formulation under the generic name adalimumab, and a Phase III program was successfully concluded in the early years of the third millennium. Included in the Phase III program were a trial in patients with incomplete response to methotrexate (MTX), where the addition of adalimumab demonstrated clinical responses that were significantly better than placebo and at par with those seen with the anti-TNF agents that had been approved up to that point, and with a dose optimum at 40 mg every other week [9]; a study where adalimumab was given in addition to background therapy with various disease-modifying antirheumatic drugs (DMARDs) with similar efficacy to the first trial [10]; a study where adalimumab as monotherapy also demonstrated efficacy, and in this study a small additional benefit (not statistically proven) was seen for 40 mg given weekly as compared to 40 mg given every other week [11]; and a study in patients on MTX where the radiographic efficacy of adalimumab was the primary outcome [12]. As had previously been demonstrated for other anti-TNF agents, the combination of MTX and adalimumab proved to be highly effective at preventing the progression of radiographic joint damage (Figure 4.2).

Subsequent to regulatory approval in 2003–04 adalimumab rapidly became one of the most widely used biologic antirheumatic agents, eventually leading the market in the US and becoming one of the top-selling medications worldwide. Following its approval for RA, it was also approved for various other inflammatory musculoskeletal diseases including juvenile inflammatory arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and more recently non-radiographic axial spondyloarthropathy (nr-axSpA). Adalimumab is also approved for diseases outside rheumatology including Crohn's disease and psoriasis.

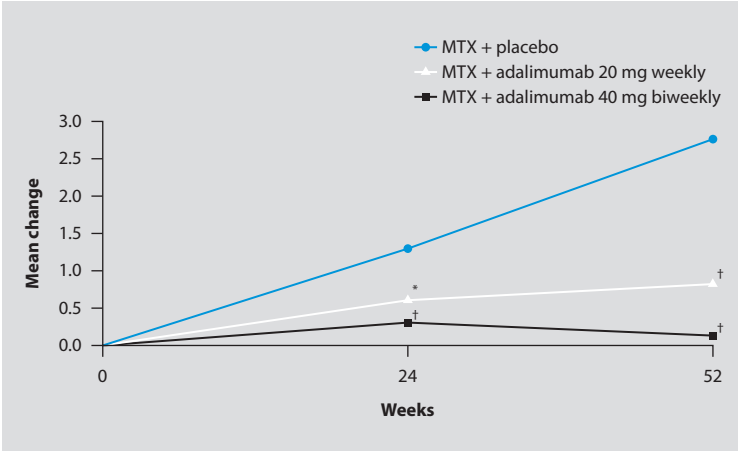

Figure 4.2 The radiological efficacy of adalimumab was demonstrated in the trial by Keystone et al. While patients on MTX plus placebo have a clear linear radiological progression (open circles), the combination of MTX and the anti-TNF agent almost completely abolishes this (closed triangles, 20 mg weekly; closed squares, 40 mg every other week). Reproduced with permission from © John Wiley and Sons, 2004. All rights reserved. Keystone et al [12].

Important studies done with adalimumab following its introduction to the market have included the Premier and Optima trials in early RA. In these trials, adalimumab was given as the first line of treatment rather than following the failure of one or more antirheumatic therapies, as originally indicated. The Premier trial demonstrated that clinical outcomes with adalimumab as monotherapy were generally not better, and in some cases worse, than with MTX as monotherapy, and both trials showed that the combination of MTX and adalimumab achieved the highest percentages of responders [13]. Importantly, nearly half the patients in the Premier trial achieved a DAS28-defined remission with combination therapy as opposed to only around one-fourth with either monotherapy. These results ensured the regulatory approval of adalimumab as a first-line therapy for RA. However, first-line treatment of newly diagnosed RA with biologics is not supported by most expert recommendations. The reasons for this and further implications will be discussed in more detail in Chapter 8.

The approved dose of adalimumab is 40 mg given once every other week. Regulatory approval also includes the use of 40 mg given weekly

in patients on monotherapy; however, very few data actually support this use, and with higher risks [14] and at double the cost this dosage should probably not be used. Remarkably, there is no adjustment of adalimumab dosing for body weight or size, nor for age or metabolic status (other than a general remark for advanced renal failure). Therefore, it should perhaps not come as a surprise that some recent studies suggest that lower dosages may be adequate for maintaining clinical responses once they have been obtained (discussed in detail in chapter 8).

Certolizumab pegol

Certolizumab pegol (Cimzia; previously CDP870) is one of the two most recently approved anti-TNF agents (Box 4.1). Although the suffix '-mab' might suggest that this is a monoclonal antibody, the molecule in fact consists of only the Fab' fragment of an anti-TNF monoclonal antibody originally designated as CDP571, linked to polyethyleneglycol (PEG) molecules that lend it greater stability and a longer half-life. Thus, this construct has several features that set it apart from the anti-TNF monoclonals: it has only a single antigen binding site, and would therefore not be expected to cross-link; it has a somewhat smaller molecular weight, which could lead to more rapid tissue penetration; it lacks the Fc portion of the immunoglobulin molecule, so that it cannot bind to Fc receptors or rheumatoid factor, nor activate complement; and it includes polyethylene glycol (PEG), which has no known biologic effects. On the whole, one might have predicted that this molecule would have noticeable differences compared with monoclonal anti-TNFs in terms of efficacy, safety, or both; but results in clinical trials so far have indicated that the drug is remarkably similar to the other TNF antagonists in these regards.

An important detail about certolizumab is that it is produced in *Escherichia coli* rather than in the CHO cells that are used for most therapeutic monoclonal antibodies. This should theoretically provide for a simpler production process and lower cost of goods, which has not changed the fact that prices of all approved anti-TNFs are remarkably similar.

Certolizumab was approved on the basis of three Phase III clinical trials: the Rapid-1 [15] and Rapid-2 [16] clinical trials in patients with RA who had an incomplete response to MTX and where certolizumab versus

Box 4.1 | Historical vignette

The background history of certolizumab is rather remarkable. During the 1980s, the British company CellTech developed the monoclonal anti-TNF CDP571 based on the hope that such a treatment would benefit patients with septic or endotoxemic shock. Unfortunately, several trials demonstrated either no or only very limited efficacy in this setting, and the development of this treatment was discontinued. Later, when Sir Ravinder Maini and Sir Marc Feldmann at the Kennedy Institute in London had developed the hypothesis that anti-tumor necrosis factor (TNF) therapy could be beneficial for the treatment of rheumatoid arthritis (RA), they approached CellTech with a request to use their anti-TNF as therapy in a first proof-of-concept clinical trial. However, the company refused, and the investigators turned to the US based company Centocor who had developed a similar monoclonal antibody designated at the time as cA2 and later named infliximab. The first trials with this molecule in RA yielded dramatic results, and a new era in the treatment of RA had been ushered in. CDP571 remained on the shelves at Celltech. Years later the successor compound CDP870 was developed and named certolizumab pegol. What became the fifth anti-TNF to reach the market could well have been the first.

placebo was added to background MTX; and the Fast4ward trial [17] in patients who had failed DMARD therapy and where certolizumab was compared with placebo as monotherapy. All three trials demonstrated convincing efficacy for certolizumab over placebo: American College of Rheumatology (ACR)20 responses in the Rapid trials were in the 60% range compared with 20% for placebo, and other outcomes also showed significant efficacy (Figure 4.3) [18].

The onset of action was noted to be quite rapid, with separation between the responses to active drug and placebo occurring within the first two weeks. It was also noted that a plateau of response was seen

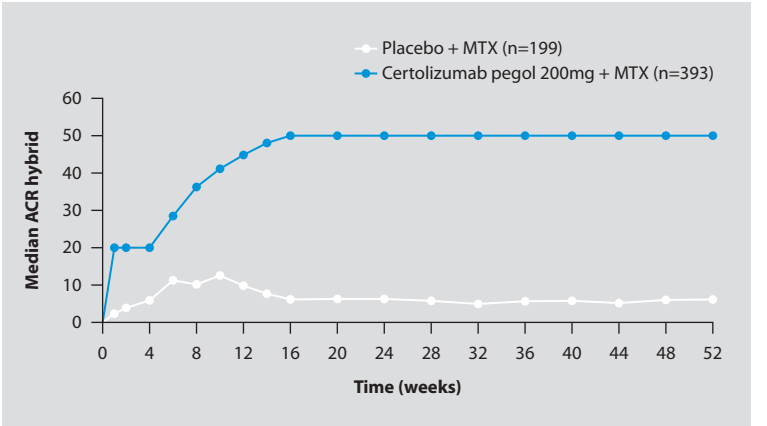

Figure 4.3 The efficacy of certolizumab pegol as reanalyzed using the American College of Rheumatology-hybrid outcome. Clear separation between active treatment and placebo is seen. ACR, American College of Rheumatology; MTX, methotrexate. Reproduced with permission from © John Wiley and Sons, 2011. All rights reserved. van Vollenhoven et al [18].

after 12 weeks, at least for the ACR20 response, suggesting that a trial period of 12 weeks is adequate to determine if certolizumab is efficacious. The use of certolizumab in combination with various DMARDs other than MTX is supported by the Phase IV Realistic trial [19].

Safety aspects with certolizumab were largely similar to those seen with other anti-TNFs. The reactivation of tuberculosis was noted relatively often but it was recognized that major cohorts of patients in the Rapid trials were recruited in countries with high prevalence of latent tuberculosis and/or relatively high risks of de novo exposure to *Mycobacterium tuberculosis*, such as Russia. The incidence of other infections during the clinical trials with certolizumab was somewhat higher than in the placebo groups, but comparable to that seen with other anti-TNF agents. A systematic review appeared to show higher risks for infection with certolizumab compared with the other TNF inhibitors [20], but weaknesses in the analyses and major differences between the various trials make it plausible that a true difference is small if one exists at all.

Certolizumab is approved as a single bi-weekly subcutaneous 200 mg injection or alternatively as two injections given every four weeks (the same total dose) in patients on background MTX; only the latter dose is

approved for monotherapy. A 'loading dose' is indicated, meaning a double dose for the first three injections; this was employed in all Phase III studies but it was never formally proven to be necessary.

Etanercept

Etanercept (Enbrel) was one of the first two approved anti-TNF treatments and continues to be one of the two leading biologics for RA and other autoimmune diseases in the world. Etanercept is not a monoclonal antibody but a receptor construct: it was genetically engineered by coupling the two copies of the naturally occurring p75 TNF-receptor to an immunoglobulin (Ig)G framework, yielding a bivalent TNF-binding molecule with similarities to monoclonal antibodies but also some differences. Specifically, etanercept is derived from fully human peptide sequences and could therefore be less immunogenic (although the joining region between the molecules does, in theory, consist of novel epitopes). In addition, it is less capable of activating various effector pathways and it binds not only to TNF but also to lymphotoxin, a different cytokine that was formerly designated as TNF-β.

The pivotal trials with etanercept were completed during the 1990s and were, by today's standards, rather small. Nonetheless, they showed convincing efficacy compared with placebo both as monotherapy and in combination with MTX [21,22]. A trial in early RA showed that etanercept was similarly efficacious to MTX but with a faster onset of action and better slowing of radiological progression [23].

Several important Phase IV clinical trials have provided additional information on the clinical efficacies of etanercept. The Tempo trial demonstrated that the clinical efficacy of etanercept as monotherapy was not or only marginally better than that of MTX in patients who were naive to the latter drug, but also that the combination of the two was more effective, particularly at achieving 'high-end' outcomes such as the ACR70 or Disease Activity Score (DAS)28-defined remission (Figure 4.4) [24].

The radiological efficacy (the ability of the treatment to prevent progression of joint erosion and joint-space narrowing) was superior for etanercept monotherapy compared with MTX and was even more impressive for the combination. By contrast, the Empire trial [25] did not clearly

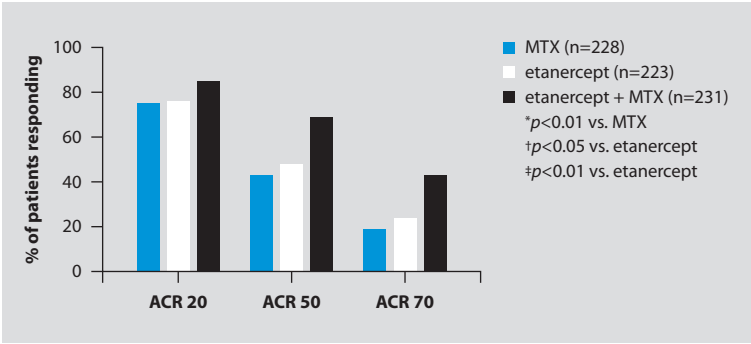

Figure 4.4 Efficacy of etanercept in methotrexate-naive patients with rheumatoid arthritis. The clinical outcomes with the combination of MTX plus etanercept are significantly superior to either monotherapy, and the difference is most notable for the 'high-end' outcomes such as ACR70. ACR, American College of Rheumatology; MTX, methotrexate. Reproduced with permission from © Elsevier, 2004. All rights reserved. Klareskog et al [24].

demonstrate the benefit of early combined treatment when compared with MTX alone, except for a more rapid response with the former.

The Preserve trial [26] was done in patients with moderate as opposed to high disease activity – a group of patients for whom biologic treatment is not reimbursed in the United Kingdom. Initial treatment with MTX + etanercept demonstrated, unsurprisingly, significant and convincing reductions in disease activity. More interestingly, patients who achieved sustained low disease activity after 36 weeks were randomized to one of three arms: those who continued only MTX (plus placebo), those who continued MTX plus etanercept at reduced dose (25 mg weekly), and those who continued both medications at the original dose. After an additional 52 weeks more than half of the patients on MTX alone had worsened and no longer had low disease activity. By contrast, in both groups who had continued with etanercept the majority maintained low disease activity, without a difference between the two doses. The smaller Dosera trial [27] obtained similar results, but with the important difference that this trial was done in patients who initially had high disease activity and for whom anti-TNF therapy had been chosen in clinical practice.

Finally, the recent Prize trial [28] in patients with early RA again demonstrated the favorable efficacy of MTX + etanercept and showed that continuing etanercept at half dose (25 mg weekly) maintains this

response in a majority of cases (63%), whereas MTX alone does so in 40% of cases. Of note, one third of patients in remission were withdrawn from both MTX and etanercept so that they received no antirheumatic treatment at all. Although, most of these patients experienced a disease flare, 23% remained in remission.

The safety profile of etanercept throughout the clinical trials program was generally favorable and later studies confirmed a relatively low incidence of side effects, including injection site reactions. Some of the trials suggested that mild respiratory infections were more common with etanercept, and a slightly increased risk for serious infections has emerged, as it has for all anti-TNFs, based on both clinical trial and registry data. The risk for reactivation of latent tuberculosis, which was demonstrated clearly for anti-TNF monoclonal antibodies, may also be elevated with etanercept but there has been a consistent impression throughout many observational studies that the risk may be smaller with etanercept than with the other anti-TNF medications.

The approved dosing of etanercept is 50 mg weekly as a subcutaneous injection; the earlier dosing of 25 mg twice weekly is also still sometimes used. From the above trial results it has become clear that a lower 'maintenance' dose may be sufficient for many patients. This will be discussed further in chapter 8.

Golimumab

Golimumab (Simponi) is a fully human monoclonal antibody directed against TNF. It was approved for use in RA approximately ten years after the first anti-TNF agents. Its most notable clinical feature is a long dosing interval, having been approved as a monthly subcutaneous injection. The clinical efficacy of golimumab was demonstrated in an extensive Phase III clinical trial program, where it was shown that the drug was efficacious at several dosage levels in various patient groups [29–31]. Importantly, one of the trials studied patients who had already failed another anti-TNF agent; golimumab therefore is the only anti-TNF that has proven efficacy in that patient population [32]. The radiological benefits of golimumab were not demonstrated as clearly as for some of the original anti-TNF agents. However, it has been recognized that the

demonstration of radiological benefit has become progressively more difficult because patient populations that were included in clinical trials in the 1990s had considerable radiological progression when treated with background therapy only, whereas trials completed in the first decade of the third millennium have demonstrated low levels of progression in the control groups. As a result, demonstrating radiological efficacy has become more difficult on two levels. First, achieving statistical significance when comparing an effective drug with a placebo in the presence of background therapy that is already effective is more challenging. Second, the reductions that are seen in more recent trials in RA have been numerically small (even if proven statistically) and it can be argued that such small improvements are clinically less relevant.

Risks and side effects with golimumab are similar to other anti-TNF agents. Thus, screening for latent tuberculosis is mandatory, and the frequency of other infections may in general be slightly increased. The injection itself can be associated with minor local reactions. Long-term risks in the form of neoplasia or autoimmune reactions are regarded as small.

Golimumab is approved at a dose of 50 mg subcutaneously once a month. The double dose of 100 mg is also approved and may confer additional benefit. In clinical trials golimumab given intravenously was shown to be effective and well tolerated [33], and intravenous golimumab (Simponi Aria) was approved by the US Food and Drug Administration (FDA). It is not entirely clear whether the intravenous route has any clinical advantages or whether it simply represents an additional option for the patient.

Infliximab

Infliximab (Remicade) was the first anti-TNF to be tested in investigator-initiated clinical trials [34]. Under the name cA2 this monoclonal antibody, which had been developed by the US-based company Centocor in the hope of finding a better treatment for septic shock, was administered intravenously to a small group of patients at the Kennedy Institute in London, UK, where dramatic improvements were noted and documented, in some cases through the use of video filming. The first reports of these experiences were encouraging but also pointed at

a major limitation: it transpired that the effect was sustained for six or eight weeks but would eventually diminish, and that repeat dosing was associated with sometimes severe infusion reactions. The development of anti-infliximab monoclonal antibodies (often referred to as human anti-chimeric antibodies, HACA) was documented and revealed an inverse dose relationship: lower infliximab dosages were associated with a greater risk, conforming to the immunological principle of 'high-zone tolerance'. More importantly, it was demonstrated relatively early on that the co-administration of MTX with infliximab reduced the risk of developing HACA and the likelihood of infusion reactions considerably, and a major conclusion from the early studies of infliximab was that the drug should be given together with MTX [35].

The Attract trial [33], a large clinical trial in RA carried out in the 1990s, demonstrated outstanding efficacy and a good safety profile (Figure 4.5). Based on this trial alone, infliximab was approved by both the US FDA and the European Medicines Agency (EMA; formerly EMEA).

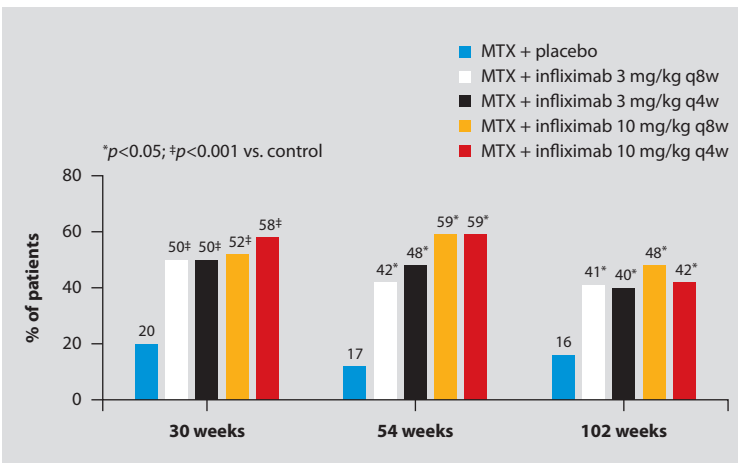

Figure 4.5 Results from the Attract trial demonstrated the efficacy of infliximab in patients with an inadequate response to methotrexate. The results were accepted by both the US FDA and the EMA (then: EMEA) as sufficient for granting approval. MTX, methotrexate. Adapted from © Massachusetts Medical Society, New England Journal of Medicine, 2000. All rights reserved. Lipsky et al [36]. Adapted from © John Wiley and Sons, 1999. All rights reserved. Lipsky et al [37]. Adapted from © Elsevier, 1999. All rights reserved. Maini et al [38].

Subsequent trials demonstrated favorable efficacy for infliximab in early RA (the Aspire trial [39]) and in many other diseases, but no further company-sponsored trials were completed with infliximab. By contrast, infliximab was the anti-TNF agent of choice in a large number of investigator-initiated clinical trials carried out over the past decade. Thus, the BeSt trial [40] compared early treatment with infliximab with three conventional strategies, and the SWEFOT trial [41,42] made the direct comparison of infliximab when added to MTX after initial failure to 'triple therapy' with the addition of sulfasalazine (SSZ) and hydroxychloroquine (HCQ). The T20 trial [43] analyzed the possibility of early treatment followed by withdrawal.

The safety of infliximab has been studied in clinical trials and in many large observational registries. The infusion itself may be associated with infusion reactions and, as already alluded to above, this was a significant problem to deal with in the early development of this agent. During the first years of the clinical use of infliximab severe infusions reactions were frequently seen, and units providing infusion treatments had to be equipped to deal with these. Remarkably, the frequency of severe infusion reactions has shown a dramatic decline over the years (Figure 4.6) [44], and it seems reasonable to speculate that improved production methods of the biologic compound are to be credited.

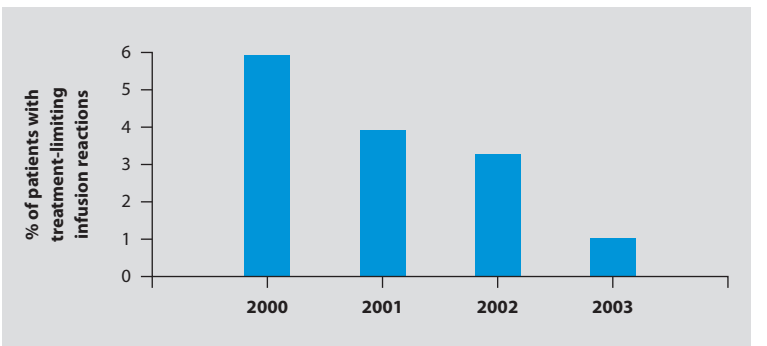

Figure 4.6 The frequency of severe infusion reactions to infliximab showed a striking decline during the first five years of use of this agent. Reproduced with permission from © BMJ Publishing Group & European League Against Rheumatism, 2007. All rights reserved. Augustsson et al [44].

Treatment with infliximab, as with all anti-TNF agents, increases the general risk of infection but the absolute risk increase is small and is mostly seen in the first year of treatment (Figure 4.7) [45].

By contrast, there is an increased risk of certain specific infections, tuberculosis being the most important one. Extensive clinical, epidemiologic, and laboratory studies have converged on the view that TNF is essential for macrophages to contain *M. tuberculosis*. Therefore, when individuals who have latent tuberculosis, ie, they harbor small numbers of mycobacteria without any clinical signs or symptoms, the risk of reactivation of the organisms is greatly increased. For all anti-TNF agents (and in fact for all biologics) screening for latent tuberculosis is therefore required, and such vigilance has clearly shown to decrease the incidence of reactivation of tuberculosis. In addition, the risk of de novo infection with *M. tuberculosis* may also be increased, but the absolute risk for this is entirely dependent on the prevalence of open tuberculosis. Other specific infections that have been linked to anti-TNF treatment (and that were identified first with infliximab) are histoplasmosis, coccidioidomycosis, and listeriosis among others.

Many studies have examined whether anti-TNF therapy is associated with an increased risk for cancer. While the risk for cancer in general does not seem to be increased, a meta-analysis of early clinical trials

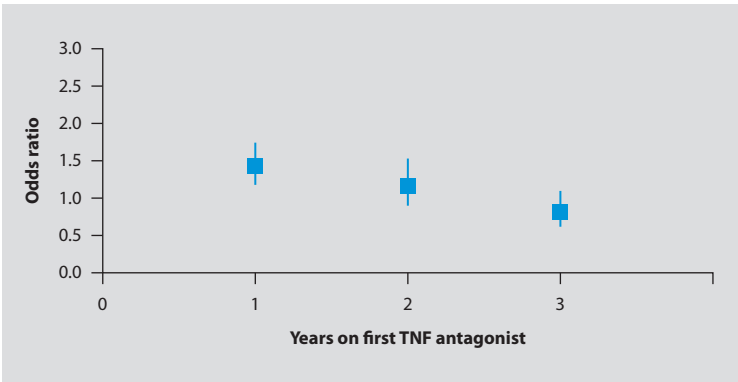

Figure 4.7 Risk for infection requiring hospitalization during the first three years of anti-TNF treatment in the Swedish national biologics registry Anti-Rheumatic Therapy In Sweden (ARTIS). TNF, tumor necrosis factor. Reproduced with permission from © BMJ Publishing Group & European League Against Rheumatism, 2007. All rights reserved. Askling et al [45].

suggested a slightly increased risk of non-melanoma skin cancer with infliximab and adalimumab, particularly at higher dosages [14], and a more recent study suggested a small but measurable increase in the risk for melanoma [46].

Other risks that infliximab shares with all anti-TNFs are the rather peculiar activations or de novo occurrences of other autoimmune diseases such as psoriasis and demyelinating disease, and 'lupus-like' syndrome. Fortunately, all of these are usually mild and reversible.

The fact that infliximab was introduced at a relatively early stage of biologics development contributed to some peculiar details of its use that persist until today:

- Treatment with infliximab is approved using a 'loading' dose: the first three infusions are to be given at 0, 2 and 6 weeks, and only thereafter is the 'usual' interval of an infusion every 8 weeks initiated. Certainly the idea of a loading dose may seem appealing, but there is no pharmacokinetic reason for a 'loading' dose in this case. There might be a pharmacodynamic reason if one were to conjecture that the amount of TNF present at the time when treatment is initiated is so overwhelming, and the ongoing production of TNF so rapid, that more drug is needed to bind to it in the early phase. However, there is no direct evidence of this, and it is possible that dosing, from the start, with an infusion every 8 weeks would be as effective as the loading strategy.
- The approved dosage for infliximab, 3 mg/kg every 8 weeks, is based on its efficacy in the Attract trial (and in some smaller, earlier trials) [33]. In that same trial a higher dose, 10 mg/kg, was also tested, and for both dosages two infusion intervals were used, every 4 and 8 weeks. With all data in hand it would seem that a slightly higher overall dose might have been more optimal, and indeed for indications such as ankylosing spondylitis a dosage of 5 mg/kg every 6 weeks is approved. However, the uncertainty in dosing and somewhat conflicting data has led to ongoing uncertainty on how to dose infliximab optimally. As pointed out, overdosing of this drug is not only a medical concern (where some increases in risk seem to be present [14]) but would also be of major economic importance.

- The fact that infliximab was approved only in combination with MTX was solidly based on the initial findings of immunogenicity when used as monotherapy. However, it is not clear that this concern has persisted unmodified over the years. As already mentioned, Augustsson et al [44] showed that during the years following the original approval of infliximab a dramatic decrease was seen in the occurrence of major infusion reactions at one large university center. Undeniably, the production process of biologics has undergone major technical improvements over the decades, and it is possible that many of the infusion reactions that occurred early on were directed at macromolecular aggregates or various forms of impurity. Moreover, the use of infliximab in other diseases has often been as monotherapy (and in the case of inflammatory bowel diseases, without MTX) and infusion reactions have gradually become much less of a clinical problem.

Infliximab biosimilars

The first infliximab biosimilar for the treatment of RA was approved by the EMA in 2014. Approval for the same product was granted to two companies, which use separate brand names, so that rheumatologists may be able to use one of two products: Inflectra and Remsima.

The mechanisms for, and the clinical implications of, approval of a biosimilar for rheumatic diseases has led to extensive discussions. The regulatory requirements for marketing approval in Europe include extensive pharmacologic and technical data in addition to a single randomized double-blinded trial that demonstrates that the biosimilar product has the same clinical efficacy and safety as the originator product in one of the approved diagnoses. Thus, for the infliximab biosimilar it was demonstrated that it was equivalent in its clinical effects to infliximab in RA [47]. Approval for several other indications was then granted based on the proven similarity rather than on separate trials.

The impact of the approval of a biosimilar on the rheumatologic therapy landscape has yet to be seen. In Norway, where the infliximab biosimilar was introduced in practice in early 2014, a tender system led to the drug being chosen among all the biologics for first-line biologic

use in new patients, based on a pricing differential of up to 39%. The use of biosimilar infliximab over the year skyrocketed and it became clear that many physicians or healthcare providers had made the decision to 'switch' patients from originator to biosimilar infliximab. It is possible that the same will occur in many other countries once this or another biosimilar is approved.

It is important to recognize that the pricing difference between a biosimilar and its originator will not be as dramatic as can sometimes be the case for generics of conventional pharmacological products. In the latter cases, pricing differences of 90% are not unusual. This will not be so for biosimilars, in part because biologics come with high costs for the production itself, but also because in the economics of the pharmaceutical marketplace the number of patients that will be treated with a drug is clearly one of the determinants of the pricing. Although the rheumatologic indications are important and not uncommon, it is a smaller market compared with anti-hypertensive therapies and statins, for example.

Immunogenicity with anti-tumor necrosis factor biologics

As indicated above, immunogenicity was an early concern in the development of the first anti-TNF agent infliximab. The mandatory combination with MTX for this biologic was based largely on the finding that immunogenicity was reduced in this situation [35]. Likewise, the early development of adalimumab was based much on the notion that a fully human molecule would have the advantage of reduced immunogenicity. However, as the occurrence of infliximab-related infusion reactions became less of a clinical concern [35,44] attention shifted to the question of whether immunogenicity could cause secondary loss of efficacy. The latter is observed clinically and the impact on biologic treatment can be dramatic, but accurate assessment and differentiation from partial efficacy and other confounding factors remains difficult [48]. Moreover, many investigators have studied the occurrence of anti-drug antibodies in patients on biologic treatments with somewhat divergent results, depending in part on methodology chosen and on interpretation. In a series of elegant papers, Wolbink and co-workers demonstrated the rather frequent occurrence of anti-drug antibodies in patients treated

with monoclonal anti-TNF agents, and the less frequent occurrence in patients receiving the receptor construct, etanercept. They also showed that the clinical efficacy of anti-TNF agents may correlate with the occurrence of anti-drug antibodies [49–52]. Longitudinal observation studies in cohorts have suggested that 'survival-on-drug' (the degree to which patients stay on a treatment) is higher for patients treated with etanercept than for some of the monoclonal agents [53], and a link between this observation and the occurrence of anti-drug antibodies has been presumed. It is possible that measurement of anti-drug antibodies could be of use in the clinical setting; unfortunately, the practical implementation of this idea has been difficult. To date, it would seem that the divergence of methods and difficulties of interpretation make it less likely that monitoring of anti-drug antibodies will become a useful tool in the rheumatology clinic. By contrast, the measurement of drug levels (therapeutic drug monitoring, TDM) is becoming more established and is likely to have clinical utility.

Interleukin-6 inhibitors

Importance of interleukin-6 in inflammation

Interleukin 6 (IL-6) is a cytokine with multiple biologic effects on inflammation but also on cellular metabolism and hepatic functions. It contributes to B- and T-cell activation, synoviocyte stimulation, osteoclast maturation, and production of acute-phase proteins. The important role of IL-6 in the inflammatory process led investigators to speculate that blockade of this cytokine could be a beneficial therapeutic principle in inflammatory diseases including RA. The first clinically effective monoclonal antibody targeting the IL-6 pathway, tocilizumab, was originally developed in connection with Japanese research exploring the role of IL-6 in multiple myeloma, thence the original name of this molecule 'myeloma-related antibody' or MRA. A large Phase II clinical trial was performed in RA and showed good dose-dependent efficacy and an acceptable safety profile [54], and a full Phase III program eventually led to the approval of tocilizumab for the treatment of RA. Additional monoclonal antibodies that target the IL-6 pathways are currently in late-stage clinical trials for RA.

Tocilizumab

Introduction

Tocilizumab (Actemra/Roactemra) is a humanized monoclonal antibody that targets the IL-6 receptor (IL-6R). The IL-6R system is more complicated than most cytokine receptors: although the IL-6R is normally bound to the cell surface, it is released from there to become a soluble receptor, and binds its ligand in the liquid phase. The IL-6/IL-6R complex then returns to the cell membrane where it is bound and triggers intracellular activation signals. Tocilizumab binds to the soluble IL-6R and thereby prevents binding to the cell membrane so that the proinflammatory signal is prevented. Tocilizumab was originally formulated for intravenous use; a subcutaneous form was later developed.

Tocilizumab efficacy

The tocilizumab Phase III clinical trial program was extensive. In separate large randomized double-blinded trials the drug was shown to be effective in patients who had an incomplete response to MTX [55] or to other DMARDs [56,57], in patients who had an incomplete or no response to an anti-TNF agent [58], and in patients who had not yet been treated with MTX [59]. In each of these trials two dosages of tocilizumab were tested: 4 mg/kg and 8 mg/kg, each given every 4 weeks. The clinical efficacy of both dosages compared with placebo was numerically comparable to that seen in similar trials with anti-TNF. One trial was designed specifically to investigate the radiologic efficacy of tocilizumab and demonstrated significant slowing of radiologic progression [60], although, as discussed earlier, this trial also suffered from the 'problem' that contemporary patient groups with RA have limited progression on control therapies. The onset of action of tocilizumab is relatively rapid and efficacy is maintained well, at least in the medium-to-long term.

Following approval of the drug some additional clinical trials were completed with interesting results. In the Adacta trial [61], patients who had active RA and who were not on MTX, because of previously documented intolerance or for other compelling reasons, were randomized to tocilizumab versus adalimumab as monotherapy. After 6 months, the

clinical results with tocilizumab were slightly but significantly better than with adalimumab (Figure 4.8).

In the Function trial (Burmester, submitted) patients who were MTX-naive were randomly assigned to MTX, tocilizumab at the lower (4 mg/kg) or higher (8 mg/kg) dose, or a combination of both. The clinical efficacy of tocilizumab was superior to that of MTX, but numerically the biggest improvement occurred with the combination of MTX plus higher dose tocilizumab. This trial also confirmed the radiologic efficacy of tocilizumab.

In several trials [62–64] it was shown that subcutaneously administered tocilizumab is similarly effective and safe when compared to the intravenous form, resulting in the subcutaneous formulation being approved for use both in the US and in Europe.

Tocilizumab safety

The safety profile of tocilizumab in the individual trials was good without any major or unexpected safety signals. Long-term safety analyses of patients, who after being in one of the randomized trials continued treatment with open-label tocilizumab in extension programs, exhibited stable low levels of adverse events [65]. The safety profile of tocilizumab (and other IL-6 antagonists) reveals some similarities but also important differences

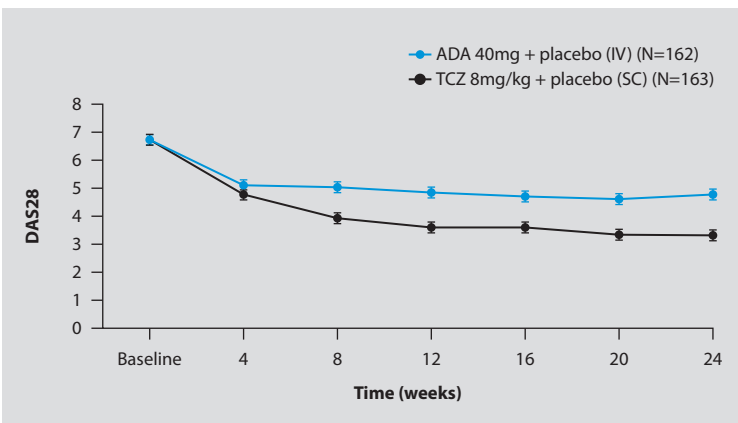

Figure 4.8 The Adacta trial demonstrated that the interleukin-6 antagonist tocilizumab as monotherapy was superior to adalimumab as monotherapy. Adapted from © Elsevier, 2013. All rights reserved. Gabay et al [61].

with anti-TNF agents. More specifically, just as is the case for most immunomodulatory therapies there is a small increase in infections, and a long-term effect on the risk for cancer cannot be excluded. Reactivation of latent tuberculosis has occurred with tocilizumab although not at the same frequency as reported with anti-TNF therapies. Nevertheless, screening for (latent) tuberculosis prior to initiating treatment is mandatory.

There are several adverse events and risks that differentiate anti-IL-6 therapies from other biologics:

1. Elevated transaminases occur at a higher frequency with tocilizumab than with other agents and can in some instances be severe, although outright hepatic failure did not occur in the clinical trials program. This kind of risk necessitates close monitoring of the patient with blood tests, and it should be emphasized that the absence of more severe consequences (liver failure) during clinical development is seen in the context of patients being closely followed.
2. Cytopenias, particularly leukopenia, neutropenia, and also thrombocytopenia occur with tocilizumab therapy and can sometimes be severe, necessitating monitoring during therapy. Again, in the clinical trial program no or very few consequences of these laboratory abnormalities were noted, but in the clinical trial setting patients are closely monitored through blood tests and if or when abnormalities are noted prompt and specific action is mandated by the protocol.
3. Elevations of cholesterol: a consistent increase in serum cholesterol levels is seen in patients treated with anti-IL6 agents. The increase is seen in both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, yielding a stable or only slightly changed atherogenic index. The long-term consequences of these lipid alterations are unknown. In the long-term safety follow-up of patients who originally participated in the clinical trials there was no increase in cardiovascular events [65].
4. 'Masking' of the acute phase response: the production of C-reactive protein (CRP) by the liver is stopped almost completely when IL-6 is blocked, and indeed when patients are being treated with tocilizumab

or other IL-6 antagonists their CRP is often at the lowest detectable level. Obviously this decrease is not only a result of decreased joint inflammation but reflects the direct and specific action of IL-6 blockade on the acute-phase response. In theory, the suppression of CRP could introduce a difficulty in the clinical work-up of new symptoms, in that healthcare providers will not be able to rely on a frequently used marker for infections. There are no studies that clearly document such a risk but it is important for healthcare providers to be aware of this issue, particularly in the acute-care setting.

Tocilizumab dosing

Intravenous tocilizumab was approved at either 4 or 8 mg/kg given at 4-week intervals. Remarkably, US and European regulators took different approaches to the specific dosing approval. Thus, in Europe the approval is for 8 mg/kg and a dose reduction to 4 mg/kg can be used in cases of side effects. In the US, the initial dosage is 4 mg/kg and it can be increased if the response is incomplete after several infusions. It is somewhat unclear how big the added benefit is of the 8 mg/kg versus the 4 mg/kg dose, and while in the individual patient the flexibility of these dosages can be an advantage, significant numbers of patients could be receiving more tocilizumab than is really needed, especially in those European countries where medications are fully paid for by insurers or healthcare systems.

The more recent approval of the subcutaneous formulation is at a dose of 162 mg given once weekly. As is the case for all the subcutaneous biologics there is no dose adjustment for body weight. How the two forms of administration compare in practice is not entirely clear. It seems likely that patients who start the treatment will more often be prescribed the subcutaneous form, all other things being equal. However, as cost considerations are increasingly influencing prescribing behavior it is possible that intravenous tocilizumab will remain the preferred choice for patients with lower body weights.

Other interleukin-6 antagonists

Several other monoclonal agents targeting the IL-6 pathway are currently in development for RA and other diseases. Sarilumab is a fully human

monoclonal antibody that binds to the IL-6R in a manner similar to tocilizumab. The efficacy and safety of sarilumab were studied in a Phase II study in patients with RA with an insufficient response to MTX. The study met its primary endpoint with the sarilumab groups achieving significantly greater ACR20 responses after 12 weeks compared with placebo [66]. Subcutaneous sirukumab, an anti-IL-6 monoclonal antibody, was also reported to be effective and safe in a recently published Phase II trial [67]. Olokizumab, a humanized anti-IL-6 monoclonal antibody, was associated with significantly greater reductions in DAS28 compared with placebo in RA patients who had previously failed TNF inhibitor therapy [68]. Yet another IL-6 blocking agent, clazakizumab was associated with rapid and significant improvements in disease activity in patients with an inadequate response to MTX [69]. All these agents appear similarly effective and safe as compared with tocilizumab.

Interleukin-1 inhibitors

Interleukin-1

IL-1 was, as the name implies, the first of the interleukins to be identified. It was initially described as the 'endogenous pyrogen'. In classical animal experiments, it was shown that an exogenous fever-causing substance (for example, lipopolysaccharide) not only causes fever but also induces the production of a different substance in the serum which, when injected into another animal, caused fever in the recipient as well. Monocytes and macrophages were identified as the cells most capable of producing IL-1, and further studies revealed the existence of specific IL-1 receptors and also of a specific antagonist: the IL-1 receptor antagonist (IL-1RA) that is believed to help in controlling the inflammatory response in the physiological setting (Figure 4.9). IL-1RA was cloned and developed into one of the first biologic agents anakinra (Kineret). Later, the monoclonal antibody canakinumab, which targets IL-1, and the IL-1 receptor construct rilonacept were also developed.

Studies of the synovial pathology in RA identified the presence of IL-1 (along with TNF) as a marker that is indicative of macrophage and macrophage-like synoviocyte activation, and it was reasonable to speculate that blockade of the IL-1 pathway would be of benefit to

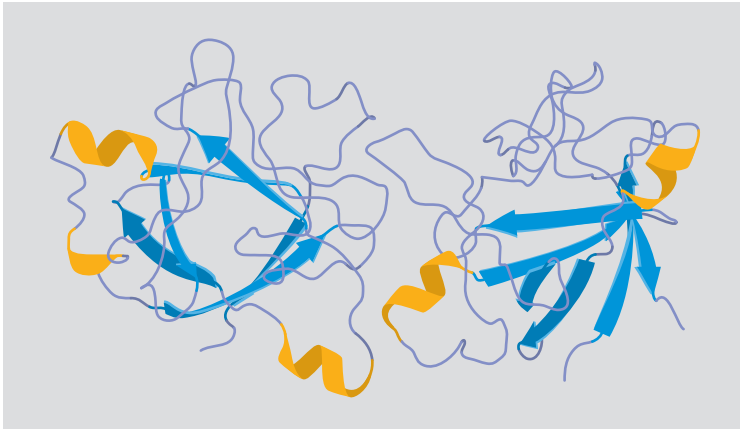

Figure 4.9 The structure of the interleukin 1 receptor antagonist (IL-1RA), a naturally occurring antagonist of IL-1. It was cloned to become the biologic treatment anakinra.

patients with this disease. Thus, a large clinical trial program in RA was started with anakinra, and these trials suggested good efficacy [70–73]. Eventually the drug was approved for the treatment of RA, but results in practice were disappointing. This may in part have been due to a true difference in efficacy when compared to anti-TNF. Data from clinical trials suggest somewhat less robust responses with anakinra, and the onset of action may be slower; however, no head-to-head trials have ever been performed. It is also possible that one of the main reasons for the failure of anakinra in RA therapy had to do with the inconvenience of daily subcutaneous injections, something few patients with RA are prepared for, and perhaps even more so, the frequency of moderate or severe cutaneous reactions to the drug. It remains possible that an IL-1 antagonist with a more acceptable dosing schedule and less frequent side effects would have fared better.

Interestingly, some observers suggested that anakinra was less effective in RA than anti-TNF because it was not as effective an antagonist of IL-1 as the anti-TNF agents were of TNF. However, this explanation was disproven when it was demonstrated that anakinra had outstanding efficacy in the cryopyrin-associated inflammatory syndromes, a group of rare diseases that are caused almost entirely by the inappropriate

production of IL-1, such as the Muckle-Wells syndrome [74], neonatal-onset multisystem inflammatory disease (NOMID) [75], chronic infantile neurological cutaneous and articular (CINCA) syndrome [76] and others. Therefore, a more plausible explanation of the less impressive efficacy of anakinra in RA is that IL-1 is simply not as important a cytokine in the pathophysiology of RA as TNF or IL-6.

Two trials examined whether anakinra in combination with etanercept could provide improved efficacy [77,78]. Unfortunately, both trials resulted in a high incidence of severe infections and the combination should not be used.

Therefore, at present, there is only a limited role for IL-1 antagonism in the treatment of RA. The other IL-1 antagonists that are currently available, canakinumab (Ilaris) and rilonacept (Arcalyst), are approved for indications other than RA and their role in the treatment of RA is currently not being investigated.

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