Ronald F van Vollenhoven

Biologics for the Treatment of Rheumatoid Arthritis

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ISBN 978-3-319-13107-8 ISBN 978-3-319-13108-5 (eBook)
DOI 10.1007/978-3-319-13108-5
Springer Cham Heidelberg New York Dordrecht London

Adis is a brand of Springer
Springer is part of Springer Science+Business Media (www.springer.com)

Project editor: Laura Hajba

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Author biography

Professor Ronald F van Vollenhoven is Chief of the Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID) at the Karolinska Institute, and of the Clinical Trials Unit Rheumatology at the Karolinska University Hospital. He received his MD and PhD degrees from the University of Leiden in The Netherlands. After graduating in 1984 he pursued immunology research at Cornell Medical College in New York, followed by a residency (specialty training) in internal medicine at the State University of New York at Stony Brook, and a fellowship in rheumatology at Stanford University in Palo Alto following which he received American Board of Internal Medicine certification in both internal medicine and rheumatology. From 1993 to 1998 Professor van Vollenhoven held a faculty appointment as Assistant Professor of Medicine in the Division of Immunology and Rheumatology at Stanford University, and from 1995 he was the Medical Services Chief and Fellowship Director in that division. In 1998 Professor van Vollenhoven moved to Stockholm, Sweden, where he worked as a Senior Physician and Chief of the Clinical Trials Unit in the Department of Rheumatology at the Karolinska University Hospital and Associate Professor of Rheumatology; and in 2010, he was appointed in his current position as Professor and Unit Chief at the Karolinska Institute.

Professor van Vollenhoven's research interests focus around the development and systematic evaluation of biologic and immunomodulatory treatments for the rheumatic diseases. With his co-workers, he has established the Stockholm registry for biological therapies (the STURE database) for this purpose, which has supported research projects relating to clinical efficacy, pharmacology, outcomes, and pharmacoeconomics. He has been principal investigator in many clinical trials of novel therapies in rheumatic diseases and has contributed to a number of important investigator-initiated trials including the SWEFOT trial. He has published over 240 original papers, book chapters and reviews, and is Editor of the textbook *Targeted Treatment of the Rheumatic Diseases* and associate-editor

of Dubois' *Lupus Erythematosus*. In 2004, Professor van Vollenhoven was awarded the Scandinavian Research Foundation Prize for excellence in clinical research in rheumatology, and he is an honorary member of several rheumatology societies. He is the Editor-in-Chief of *Lupus Science & Medicine*, Chair of the EULAR Standing Committee on Clinical Affairs, member of many editorial boards, past-chair of the Swedish Rheumatology Society Professors' Council, co-founder of the IRBIS registry for biologics in systemic lupus erythematosus (SLE), the CERERRA registries collaboration, and the NORD-STAR collaboration for Nordic trials in the rheumatic diseases, and the initiator of the Treat-to-Target-in-SLE initiative. Professor van Vollenhoven lives just north of Stockholm with his wife and children aged 20 and 16. Outside his professional life he is an avid classical pianist.

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Abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ANCA	Anti-**n**eutrophil **c**ytoplasmic **a**utoantibody
APC	Activated protein C
AS	Ankylosing spondylitis
ASA	Acetyl-salicylic acid
axSpA	Axial spondyloarthropathy
AZA	Azathioprine
BCG	Bacillus Calmette-Guérin
bDMARDs	Biological DMARDs
CDAI	Clinical Disease Activity Index
cDMARDs	Conventional DMARDs
CHO	Chinese hamster ovary cell
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CLL	Chronic lymphocytic leukemia
Cox	Cyclo-oxygenase
CRP	C-reactive protein
CTLA-4	Cytotoxic T lymphocyte-associated molecule 4
CyA	Cyclosporine A
DAS	Disease Activity Score
DMARDs	Disease-modifying antirheumatic drugs
EIRA	'Epidemiology in RA'
EMA	European Medicines Agency
EPO	Erythropoietin
EQ5D	EuroQuol5D
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GC	Glucocorticoids
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HACA	Human anti-chimeric antibodies

HAQ	Stanford Health Assessment Questionnaire Disability Index
HCQ	Hydroxychloroquine
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HR-QOL	Health-related quality of life
HSTCL	Hepatosplenic T-cell lymphoma
IBD	Inflammatory bowel disease
Ig	Immunoglobulin
IL	Interleukin
IL-1RA	IL-1 receptor antagonist
IL-6R	IL-6 receptor
IFN γ	Interferon γ
JAK	Janus kinase
JIA	Juvenile inflammatory arthritis
LDL	Low-density lipoprotein
MAP	Mitogen-activated protein
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MTX	Methotrexate
NICE	The National Institute of Clinical Excellence
NOMID	Neonatal-onset multisystem inflammatory disease
NSAIDs	Non-steroidal anti-inflammatory drugs
PDE-4	Phosphodiesterase 4
PEG	Polyethyleneglycol
PML	Progressive multifocal leukoencephalopathy
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RADAI-5	Rheumatoid Arthritis Disease Activity Index-5
RAPID-5	Routine Assessment of Patient Index Data-5
RF	Rheumatoid factor
SAARDs	Slow-acting antirheumatic drugs
SDAI	Simplified Disease Activity Index

sJIA	Systemic juvenile idiopathic arthritis
SLE	Systemic lupus erythematosus
SSZ	Sulfasalazine
Syk	Spleen tyrosine kinase
T2T	Treat-to-Target
TCR	T-cell receptor
Th	T-helper cell
TNF	Tumor necrosis factor
TYK2	Tyrosine kinase 2
US FDA	United States Food and Drug Administration
VAS	Visual analog scale

Chapter 1

Disease overview

Rheumatoid arthritis (RA) is a chronic inflammatory disease of presumed autoimmune etiology that is characterized by symmetric inflammation of the synovial joints, which may lead to damage to the cartilage and bone and a progressive loss of function. The prevalence in Western adult populations is 0.5–1% and it is relatively similar across Europe, North America, Asia, and South Africa. However, certain native American Indians, for example Pima Indians [1], have a higher prevalence and, in contrast, RA appears to be rare in some rural African black populations [2] although not in others [3]. The annual incidence is between 0.15 and 0.88 per 1000 and women are affected two or three times as often as men. RA occurs in all age groups with a peak of disease onset between 45 and 65 years of age [4].

Clinical presentation

The clinical presentation of RA is variable but symptoms of the joints in the form of pain, stiffness and impaired movement are the cardinal features. The onset of symptoms can vary from slow and gradual to abrupt. The joint symptoms are often associated with striking morning stiffness: it may take the patients one or two hours before reaching their baseline mobility in the joints. Typically, the joint symptoms are associated with symptoms of generalized inflammation: the patient may experience abnormal fatigue and lassitude, lose weight, and have low-grade fever.

While all diarthrodial joints can be affected, the most common presentation is with inflammation in the small joints of the hands and the feet, as well as in some of the larger joints. The inflammatory process

R.F. van Vollenhoven, *Biologics for the Treatment of Rheumatoid Arthritis*,
DOI 10.1007/978-3-319-13108-5_1

leads to swelling of the synovium, which is clinically perceived as fusiform swelling around the lining of the joints (Figure 1.1).

The swelling is generally soft or doughy to palpation and associated with warmth and tenderness; in the larger joints there may be palpable effusions as well. The initial presentation with symptoms from the hands and knees is quite common. Characteristically in RA the disease is symmetric, although perhaps not at the individual joint level but certainly in terms of the affected joint groups. Although most of the spine is not usually involved in RA the cervical spine may be affected by a potentially dangerous inflammation in the C1–C2 region.

Over the course of time RA causes anatomical changes in the joints, due to damage to the cartilage and bone, which can be visualized on radiographs (Figure 1.2), as well as more subtle forms of damage to the fibrous structures of the joints and atrophy of the intrinsic musculature of the hands and feet.

The combination of these chronic changes leads to some clinically recognized patterns of deformity such as the swan-neck and boutonnière deformities of the fingers (Figure 1.3), the ulnar deviation of the hands, hammer-toe deformities in the feet, and others.

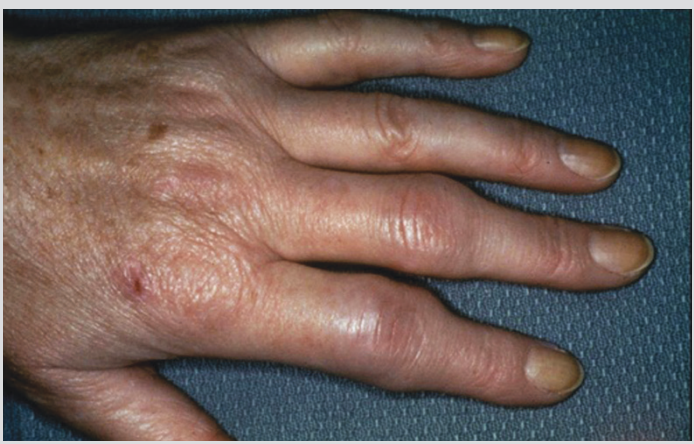

Figure 1.1 Typical swelling of the small joints of the hands in rheumatoid arthritis. The joints most frequently affected are the metacarpophalangeal and proximal interphalangeal joints. Reproduced with permission from © American College of Rheumatology, 2015. All rights reserved. American College of Rheumatology [5].

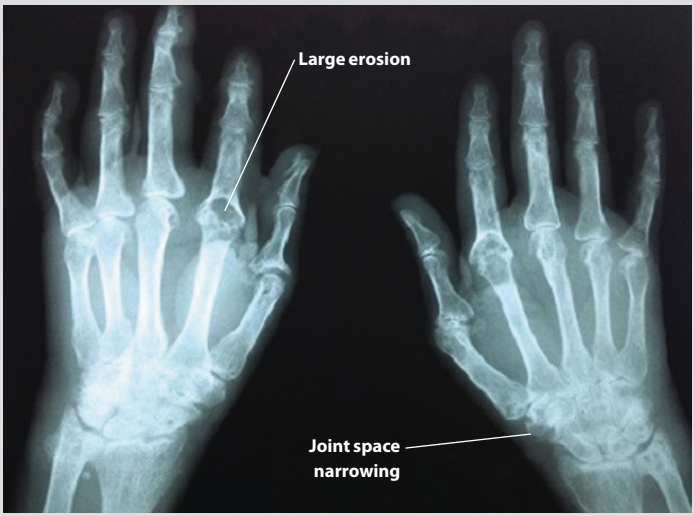

Figure 1.2 Radiograph of the hand showing characteristic destructive changes of rheumatoid arthritis: erosions of the bone and joint-space narrowing, which represents loss of cartilage. Reproduced with permission from © N Firooz, 2015. All rights reserved. Firooz [6].

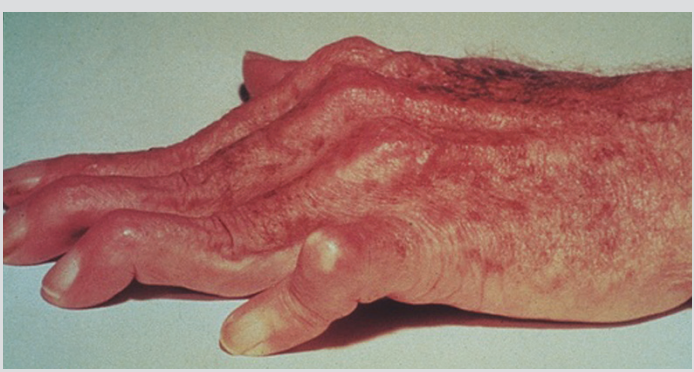

Figure 1.3 Typical deformities of the hand in advanced rheumatoid arthritis. Both swan-neck deformity (flexion contracture of the distal interphalangeal joint combined with hyperextension of the proximal interphalangeal joint; in digit III and IV) and Boutonnière deformity (flexion contracture of the proximal interphalangeal joint combined with hyperextension of the distal interphalangeal joint; in digit V) are seen. Reproduced with permission from © American College of Rheumatology, 2015. All rights reserved. American College of Rheumatology [5].

Patients with RA can also develop extra-articular manifestations such as vasculitis, nodules, sicca syndrome, and cardiac or lung involvement; these complications are seen mostly in patients with severe joint disease.

Mortality is increased in a subset of RA patients and this has been related to a high frequency of cardiovascular disease [7,8]. Thus, the impact of the disease is wide, not only resulting in decreased health-related quality of life, but also a loss of productivity and a major increase in healthcare costs [9].

Etiology and pathogenesis

The etiology of RA is believed to be multifactorial and based on unfavorable gene–environment interactions [10]. The strongest genetic risk factor for RA is the 'shared epitope', a specific sequence of five amino acids on the HLA-DRB1 molecule, while the strongest known environmental risk factor is cigarette smoking. A gene–environment interaction between the shared epitope and smoking in determining the risk of anti-citrullinated protein antibody (ACPA)-positive RA has been convincingly demonstrated [11].

Patients not uncommonly identify antecedent events as the cause or 'trigger' of their disease, but the nature of these differs from person to person: infections, trauma, and various physical, psychological, or social life events are all mentioned [12], but no convincing causal link to any of these has been established. The large controlled study 'Epidemiology in RA' (EIRA) found no major differences in the frequencies for such events between patients and controls [13], but pointed at complex interactions between genetic and environmental factors [14].

Pathophysiology of joint inflammation in rheumatoid arthritis

The central inflammatory disease process in RA takes place in the synovial membrane, which becomes inflamed and releases inflammatory cytokines, causing damage to the joint components, cartilage, and bone, and thus progressive joint destruction. The inflamed rheumatoid synovium is characterized by dense cellular infiltrates, mainly composed of macrophages, T cells and B cells. T cells play an important role in sustaining the inflammation of RA, with a predominance of T-helper (Th)

cells in the synovial infiltrate. However, activated monocyte/macrophage lineage cells also appear to play a major role, as reflected by the presence of excessive quantities of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) in the synovium [15]. Biological activities attributed to TNF include induction of proinflammatory cytokines such as IL-1 and IL-6; enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes; and activation of neutrophils [16,17]. Neoangiogenesis, the formation and growth of new capillary blood vessels, is also observed in the rheumatoid synovium and is considered a key event in the development and persistence of inflammation. Synovial cells and articular chondrocytes release the tissue-damaging enzymes metalloproteinases, which are responsible for the progressive destruction of cartilage and subchondral bone [18].

Diagnosis and classification

RA remains a clinical diagnosis based on the interpretation of the clinical symptoms and signs as well as findings on appropriate investigations by an experienced clinician. However, over the past several decades various initiatives have been taken to develop classification criteria for RA. While these criteria were intended for use in clinical research they have gradually assumed the character of diagnostic criteria, and many clinicians now rely on these in clinical practice. It remains important to recognize that in the development of such criteria, the 'gold standard' is always the expert clinician's opinion and even the best criteria will have false positives and false negatives; thus, it would be a mistake to rely exclusively on any set of criteria to diagnose RA in clinical practice.

The most recent classification criteria were developed jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) [19]. According to these criteria, the patient can be said to have RA if:

- he/she has at least one swollen joint – not explained by another disease

AND

- incontrovertible radiological evidence of the disease

OR

- at least 6 points when scored as follows:
  - involvement of 2–10 large joints (and no small joints): 1 point
  - involvement of 1–3 small joints: 2 points
  - involvement of 4–10 small joints: 3 points
  - involvement of >10 joints (including at least one small joint): 5 points
  - low positive rheumatoid factor and/or anti-citrullinated peptide antibodies: 2 points
  - high positive rheumatoid factor and/or anti-citrullinated peptide antibodies: 3 points
  - elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR): 1 point
  - duration >6 weeks: 1 point

Compared to the previous ACR classification criteria for RA these newer criteria make it possible to diagnose RA at an earlier stage, which was considered important for therapeutic trials. In practice, early diagnosis remains a challenge and minimizing both the risk of delaying the diagnosis and thereby the treatment on the one hand, and of incorrectly making a diagnosis of what is in principle a life-long disease on the other, remains a major challenge for the practicing rheumatologist.

Long-term complications of rheumatoid arthritis

Long-standing RA is typically associated with significant loss of function due to irreversible damage to the joints. In addition, patients with severe RA may have extra-articular manifestations of the disease, including some relatively benign ones such as skin nodules but also more serious ones such as interstitial lung disease, mononeuritis (multiplex), or vasculitis. RA is associated with increased mortality. Although this may in very rare cases be attributable to the disease itself, it is mostly related to the increased incidence of various morbidities in the patient with RA such as infections, cardiovascular events [7,8], and malignancies. It is believed that these increases represent the combined effect of the disease and its treatment, although for some specific long-term morbidities the associations are more clearly identified as one or the other; for example, lymphoma

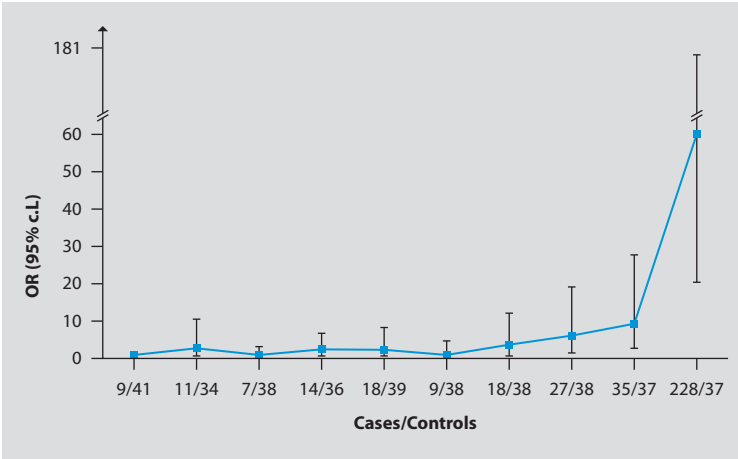

Figure 1.4 The risk of lymphoma is strongly associated with the cumulative disease activity of rheumatoid arthritis rather than with its treatment. Risk of lymphoma in relation to cumulative disease activity, assessed in 372 patients with rheumatoid arthritis (RA) and in matched RA controls. Symbols show unadjusted odds ratios (ORs); bars show 95% confidence intervals (95% CIs). Deciles of the area under the curve for cumulative disease activity are shown on the x-axis; ORs were calculated using the first decile as the reference. Reproduced with permission from © John Wiley and Sons, 2006. All rights reserved. Baecklund et al [20].

has clearly been associated with long-term and cumulative severity of the inflammatory disease (Figure 1.4) [20], and severe infections were strongly associated with corticosteroid treatment [21].

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Chapter 2

General treatment aspects

Goals of treatment

Rheumatoid arthritis (RA) is almost invariably associated with significant symptomatology. In the early stages of the disease, joint pain and stiffness are the dominant symptoms, but patients also frequently experience general symptoms due to the systemic inflammatory state. Extreme fatigue and lassitude, and even slight fever and profound weight loss are not unusual at this stage. The musculoskeletal symptoms may already in the earlier phase engender significant functional impairment and restriction of activities which are, however, still reversible. At later stages of the disease, inflammatory symptoms may continue to be severe but in contrast to more benign musculoskeletal conditions RA has the potential to cause severe and irreversible damage to the anatomical structures of the joints as well. Thus, erosions and other damage to the bony surfaces of the joints, and cartilage break-down are hallmarks of the disease that when advanced are easily recognized on plain radiographs, but that may at even earlier stages be detected through more sensitive imaging techniques such as magnetic resonance imaging (MRI) and ultrasound (Figure 2.1).

Importantly, these irreversible structural changes do not start late during the disease process, even though they are often only detected after months or years. Several lines of investigation strongly suggest that the destructive process starts around the same time as the onset of inflammatory symptoms [1–3]. A small subset of patients with RA have a disease phenotype that is striking for its limited symptoms despite very obvious

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DOI 10.1007/978-3-319-13108-5_2

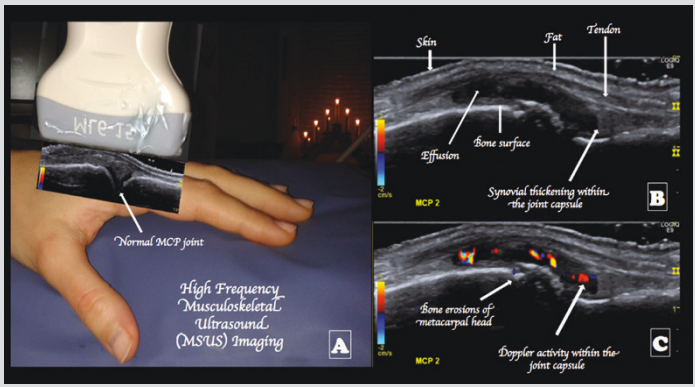

Figure 2.1 Ultrasound image of the joint, demonstrating the inflammatory process in the synovium as well as an early erosive change. Photo courtesy of Y Kisten.

signs of inflammation (synovial swelling of the joints) and destructive potential seen on radiographs. This disease phenotype is referred to as the 'robustus' type and patients in this situation may be undertreated as a result of the limited subjective symptoms [4].

From the above follow the treatment goals for RA. First, the patient's symptomatic burden must be alleviated. Patients generally see this as the most obvious and clearest goal of the treatment and will seek medical care primarily to obtain such relief. However, the important second goal must be to prevent, as much as possible, the destruction of joint structures as a result of the disease; these two goals are not always aligned. Simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) may provide some symptomatic relief but there is no evidence that they prevent joint damage. Even glucocorticoids (GCs) may, despite their strong anti-inflammatory and symptom-relieving properties, not prevent damage if used at moderate or high doses as monotherapy for RA (however, adding low-dose GCs to conventional antirheumatic treatments can provide some additional protection from damage, as will be discussed). Thus, the approach to RA must always be based on the dual goals of relieving symptoms and preventing long-term damage and resulting disability. These goals can be regarded as part of the more

extensive framework articulated by Fries [5], who identified the five dimensions of treating chronic illnesses as the 'five D's':

- death: preventing mortality;
- discomfort: relieving symptoms;
- disability: preventing functional decline;
- drug side effects: minimizing toxicities due to the treatment; and
- dollar cost: finding an appropriate health–economic balance.

In the case of RA, while mortality that is directly attributable to the disease is rare it has been shown that patients die earlier than expected from otherwise unremarkable causes, mostly cardiovascular disease [6,7], malignancies [8], and infections [9]. A contribution to these risks from both the disease itself and the treatments seems plausible, as is the belief that more effective therapies used in a judicious manner might even improve mortality.

In addition to the goals of limiting discomfort and disability, the therapeutic discussions around RA are frequently dominated by considerations of the risks from the treatments, and of costs. In fact, for biologic therapies the latter aspect has become one of the dominant themes in articulating treatment approaches for RA. Thus, having good symptom-relieving properties and having demonstrated superior abilities to prevent joint damage, the use of biologics is mostly limited by some risk considerations (but having a safety profile that compared with conventional agents is good) and by the major cost issues that their use entails.

Measuring disease activity and treatment response

Measuring disease activity

Measuring disease activity in a chronic disease such as RA is not a trivial exercise. From the patient's perspective the disease is multi-dimensional to begin with, causing various forms of subjective suffering: pain, stiffness, fatigue, lassitude, and a great many different kinds of disability. From the physician's point of view disease activity may be perceived as objective signs of joint swelling, findings on imaging that represent inflammation directly (Doppler signal on ultrasound) or indirectly (juxta-articular osteopenia on plain radiographs), or as laboratory tests that vary with inflammatory states (acute phase reactants, leukocytosis,

anemia, and thrombocytosis). For practical reasons as well as for clinical research and clinical trials it has been considered advantageous to have a single value to indicate disease activity – even while respecting the multi-dimensional nature of the disease. The most widely used method for this has been the Disease Activity Score (DAS), originally developed in the Netherlands [10]. It combines four measures: the swollen joint count, the tender joint count, the patient's global assessment, and an acute-phase reactant, into a single numerical value; the higher the value, the greater the disease activity. Several different versions of the DAS exist: the original DAS was based on a 44-joint score for swollen joints and the Ritchie articular index for tenderness, and the erythrocyte sedimentation rate (ESR), while the DAS28 uses swollen and tender joint counts based on 28 joints [11]; and either of these two can be modified to use the C-reactive protein (CRP) instead of the ESR [12]. There are also publications using a modified DAS with only three of these four components. The most widely used version, however, is the DAS28 with four components including the ESR and for this version many detailed analyses have been done. Thus, a value over 5.1 is considered a high disease activity, between 3.2 and 5.1 moderate disease activity, between 2.6 and 3.2 low disease activity, and below 2.6 a remission and these cut-offs were not simply chosen but benchmarked based on rheumatologists' treatment decisions (Figure 2.2) [13].

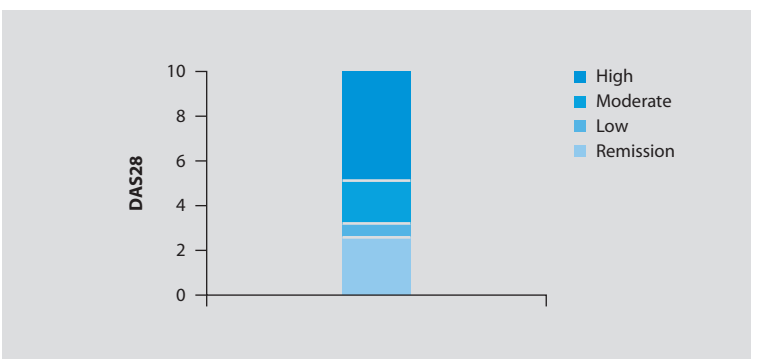

Figure 2.2 Rheumatoid arthritis disease activity based on the disease activity score using the 28 joint count (DAS28). Cutoffs are at 2.6, 3.2 and 5.1.

However, the DAS28-based definition of remission has been criticized for allowing patients to be classified as being in remission while having several swollen and/or tender joints, violating the face validity of a remission. In defense of the DAS28 instrument, it is fair to point out that the definition may still work well at the group level if as many patients with values under 2.6 are not in true remission as there are patients whose DAS28 is above 2.6 when, in fact, they are in remission; something that is certainly seen in the clinic and for which many factors can be responsible.

Several other systems for measuring disease activity have been developed. The Simplified Disease Activity Index (SDAI) uses similar components to the DAS, but is simpler to calculate [14]; the Clinical Disease Activity Index (CDAI) is based on clinical parameters only [15]. Some instruments are based entirely on the patient's report, such as the Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5) [16] and the Routine Assessment of Patient Index Data-5 (RAPID-5) [17].

For ascertaining the functional impact of RA on the patient's daily life, a considerable amount of literature exists on the use of the Stanford Health Assessment Questionnaire Disability Index, usually (although technically incorrectly) abbreviated as 'HAQ' [18]. This series of 20 questions in eight categories of functioning in daily life yields a single numerical value ranging from 0 for full physical function to 3.0 for extreme disability. For all its limitations (floor effects, ceiling effects, subjectivity, and course-graining among other considerations) the HAQ has proven to be an exceptionally useful instrument in clinical trials and even in clinical practice [19]. A slight modification of the lay-out of the HAQ (but not of the instrument itself) that is available in Sweden has made it much easier to score so that a rheumatologist can calculate the HAQ during the patient visit with hardly any loss of time. Various modified versions of the HAQ have also been developed and used in some settings [20,21]. A more extensive assessment of physical function as well as other patient-centered domains of health and disease impact is afforded by the SF-36 [22]. The simple EuroQuol5D (EQ5D) has been developed as a measure of overall health-related quality of life (HR-QOL; utility) [23]. Finally, the instrument called 'patient-reported outcome measurement system' or PROMIS [24] is an ambitious and forward-looking initiative to integrate

item response theory and computerized adaptive testing into a clinically useful instrument, with interesting results to date [25,26].

Measuring treatment response

It is not trivial to ascertain whether a patient has responded to antirheumatic treatment. Conventional disease-modifying antirheumatic drugs (cDMARDs) usually have a slow onset of action, measured in weeks to months. As the natural variability of the disease over time is quite considerable physician and patient recall cannot be relied upon accurately to determine if an improvement has occurred and, if so, how great it has been. During the second half of the 20th century many systems were devised to measure RA disease activity, and by the early 1990s this had led to considerable chaos in the area of therapeutics, with dozens of measurements being used in clinical trials. To address this issue, concerted efforts were made to identify the most reliable outcomes for determining whether a therapeutic was effective. Thanks to this work, it was determined that a core set of seven RA-related variables was useful: the number of swollen joints, the number of tender joints, the patient's own assessment of disease activity by a visual analog scale (VAS), the patient's assessment of pain by a VAS, the physician's assessment of disease activity by a VAS, the HAQ disability index, and an acute phase reactant for which either the ESR or the CRP could be used (Box 2.1) [27]. Based on these seven core set variables a system for ascertaining response to treatment was developed and adopted by the American College of Rheumatology (ACR): an improvement by at least 20% in both swollen and tender joints, and in at least three of the remaining five core outcomes, would identify the patient as a 'responder' according to what was called the 'ACR20 response criterion' [28]. The ACR20 was shown to have outstanding metric properties and to be able to distinguish the response to an active compound from a placebo better than any of the individual components or other plausible measures. Note, however, that the ACR20 response was not intended to reflect a clinically important or even clinically meaningful change, nor was it intended for use in clinical practice. Analogous improvements called ACR50 and ACR70 were later added and used extensively in clinical trials. Many experts feel that the

Box 2.1 | Historical vignette

By the early 1990s, a great number of measurements were used both in clinical practice and in clinical research. In addition to measures that are still in use today, such as joint counts and visual analog scales, more fanciful measurements were also used. Some rheumatologists used systems consisting of rings of increasing diameter to measure the swelling of each joint. Some immersed the patient's finger in a mercury bath to determine the exact volume of the swollen digit. Functional tests include times for buttoning a shirt, walking a specified distance, or for performing other tasks. Hand strength was measured with various gadgets. When a task force of the American College of Rheumatology was convened to determine how best to conduct clinical trials in RA, they counted more than eighty different measurements. It is a good thing they were able to reduce it to the 'ACR core set' of just seven outcomes.

latter measures represent more clinically relevant improvements, but the differentiation from placebo is not as good for these outcomes as it is for the ACR20.

A completely different method of ascertaining response to treatment was based on the DAS28 and adopted by the European League Against Rheumatism (EULAR) [29]. The EULAR response is based on both the interval change in the DAS28 and on the DAS28 value achieved at the end of the observation period. Thus, a patient is said to have a EULAR good response if her/his DAS28 has improved by at least 1.2 and if the DAS28 after treatment is below 3.2. A EULAR moderate response is defined as having an improvement by at least 0.6 and a DAS28 after treatment below 5.1 (with a small additional modification). Compared with the ACR20, the EULAR definition of response has some attractive features, being a little more intuitive and clinically relevant, but it may not be as sensitive for detecting treatment effects in placebo-controlled trials as the ACR20 criteria. In addition, because it has three levels of response, it can sometimes be unclear what is measured most optimally.

More recently, the explicit goal of therapy in RA has been identified as remission [30]. The definition of 'remission' has been the subject of much work, leading to an ACR/EULAR definition that presents two possibilities: a combination of four criteria that have to be fulfilled or an SDAI<3.3 (Table 2.1) [31].

The criteria definition requires that the patient has at most one swollen and at most one tender joint, a CRP that is no higher than 10 mg/L, and registers at most 1 cm on a 0–10 cm VAS scale for the patient's own global assessment. Each of these four criteria has to be fulfilled, combining them with the Boolean operator 'AND', and for this reason they are sometimes referred to as 'the Boolean remission criteria' [31]. Recent studies have pointed at some weaknesses with the definition, especially

American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials*
Boolean-based defination
At any time point, patient must satisfy all of the following: Tender joint count ≤1[†] Swollen joint count ≤[†] C reactive protein ≤1 mg/dl Patient global assessment ≤1 (on a 0–10 scale)[‡]
Index-based defination
At any time point, patient must have a Simplified Disease Activity Index score of ≤3.5[§]
*See text and tables 2 and 3 for recommendations regarding assessment of remission in clinical practice settings.
[†]For tender and swollen joint counts, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles and it is preferable to include feet and ankles also when evaluating remission.
[‡]For the assessment of remission we suggest the following format and wording for the global assessment questions. Format: a horizontal 10cm visual analog or Likert scale with the best anchor and lowest score on the left side and the worst anchor and highest score on the right side. Wording of question and anchors: For patient global assessment, 'Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?' (anchors: very well-very poor). For physician/assessor global assessment, 'What is your assessment of the patient's current disease activity?' (anchors: none-extremely active).
[§]Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale) and C reactive protein level (mg/dl).

Table 2.1 American College of Rheumatology/European League Against Rheumatism definitions of remission in rheumatoid arthritis clinical trials. Reproduced with permission from © BMJ Publishing Group & European League Against Rheumatism, 2011 All rights reserved. Felson et al [31].

the fact that the VAS of the patient can sometimes be higher due to reasons other than RA [32]. It should be noted that the remission criteria were designed first and foremost for use in clinical trials, that is, for use in analyses at the group level. The criticism that some patients may not fulfill the criteria although they are in remission, or that conversely they do fulfill the criteria while a sensible rheumatologist considers them not to be in remission, is therefore not entirely relevant: as long as these two groups of patients 'cancel out', the definition could still work well at the group level. On the other hand, because the ACR/EULAR criteria were developed with the explicit goal of minimizing 'false-positives', that is, to make the group who fulfill the criteria but are not deemed to be in remission as small as possible, it is possible that group-level analyses using these criteria will yield proportions of patients who are considered in remission that are smaller than clinical reality. In this regard, the DAS28-based remission definition may yet turn out to provide the more accurate estimates.

Overview of treatment approaches

Evolution of treatment approaches over the past two decades

Until the late 1980s, treatment options were limited with only a few specific antirheumatic agents in use. These agents were all slow-acting, and some were associated with risks of major toxicities (for example, gold salts and penicillamine). Therefore, the general approach was summarized as 'go low, go slow'. It was recommended to start treatment with acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs) and to allow a long period of time (1–2 years) to determine if this treatment was adequate. If this treatment was not adequate, smaller dosages of the specific antirheumatic therapies were initially recommended and an escalation of the treatment was only suggested after relatively long trial periods at each step. Antirheumatic medications were to be administered as single therapies and never in combination. A visualization of this approach to therapy was the 'pyramid' approach of treating RA: the base of the pyramid consisted of modalities that would apply to all patients including physical therapy, rehabilitation, and simple analgesics; above that came ASA and the NSAIDs; the next step upward, applicable to a

smaller proportion of patients, consisted of the DMARDs (then referred to as slow-acting antirheumatic agents, SAARDs); and the top of the pyramid consisted of rarely-used and/or experimental therapies for RA, such as plasmapheresis. To the sides of the pyramids were additional treatment possibilities that could be used when needed: GC injections or even GCs given orally, and rheumatologic surgery.

Several key observations made during the 1980s propelled a revision of this treatment strategy. It was recognized that irreversible damage to the articular structures occurs early in the disease course, and that DMARDs can to some extent attenuate the damage, suggesting that earlier intervention with such agents might prevent to some extent the long-term consequences of the disease. A revision of the treatment strategies was sometimes referred to as 'remodeling' or 'inverting' the pyramid [33], and the main ideas embedded in this rethinking were:

- the use of DMARDs early in the disease course;
- optimal dosages: escalating therapies more rapidly than had been customary in practice; and
- consideration of some combinations of DMARDs.

These ideas were summarized as the 'RESCUE' approach: rapid escalation, selective combinations, and consideration of unproven, experimental therapies [34].

As to the idea of combining DMARDs, this once controversial proposal was propelled to the foreground by several studies published in the early 1990s. Thus, a landmark trial by O'Dell et al [35] demonstrated that the combination of methotrexate (MTX), sulfasalazine (SSZ), and hydroxychloroquine (HCQ) was more effective than both MTX alone and the other two drugs combined. The trial also found toxicities, the main concern with combined DMARDs, to be manageable. Similarly, the combination of MTX and cyclosporine A (CyA) was tested in a randomized trial and found to be superior to MTX alone [36]. However, it should be noted that not all combination therapy trials were successful. A large randomized trial comparing MTX, azathioprine (AZA), and the combination of the two revealed that MTX+AZA was not more effective than MTX alone but was considerably more toxic [37]. Uncontrolled observational studies also revealed that even more aggressive combination therapies including

cytotoxic drugs were in some cases associated with considerable toxicities and were unlikely to result in additonal benefit [38–40].

More recently, the combination of MTX and leflunomide was studied in a large, well-controlled trial that suggested some added benefit for this combination [41,42]. However, later observations derived from practice and/or registries raised more substantial concerns regarding toxicities (in this case, liver toxicity) [42] and this combination must be considered appropriate only under close monitoring.

Overview of the non-biologic treatments for rheumatoid arthritis

The main non-biologic pharmacological treatment categories for RA are NSAIDs, GCs, and DMARDs.

Non-steroidal anti-inflammatory drugs

NSAIDs are a large group of structurally dissimilar medications that share a single mechanism of action: blockade of cyclo-oxygenase (Cox), the rate-limiting enzyme in the production of pro-inflammatory prostaglandins. Based on the original discovery of the mechanism of action of ASA by Vane, Bergström and Samuelsson, these medications have been staples in the treatment of temporary aches and pains, but also in the treatment of various localized musculoskeletal conditions such as bursitis and tendonitis. They are sometimes used to treat gout, can be effective long-term medications for spondyloarthropathies, and are widely used for osteoarthritis. However, NSAIDs have a more modest role in the treatment of RA. They should not be used as the main therapy (except perhaps in the mildest of cases) but can be added to appropriate antirheumatic treatment to achieve more optimal symptom control. NSAIDs as a class share the risk of gastric toxicity, which can lead to gastritis, peptic ulcers, perforations, and bleeding, and are therefore often combined with proton-pump antagonists, histamine 2-antagonists, or misoprostol. Another approach aimed at avoiding the gastrointestinal toxicity of NSAIDs was the development of Cox-2 specific inhibitors, which would spare the gastric mucosa. Although this was indeed proven to be the case, the unexpected finding of a potentially increased cardiovascular risk greatly reduced the enthusiasm for this class of drugs.

Glucocorticoids

GCs (corticosteroids) are highly effective in suppressing the inflammation in RA (and many other diseases) but are predictably associated with multiple side-effects if treatment is continued during longer periods of time at effective anti-inflammatory dosages. The use of GCs is therefore limited to several specific scenarios:

- High-dose GCs (0.5–1.0 mg/kg or even higher) are reserved for patients with organ- or life-threatening extra-articular complications of RA where they are usually combined with powerful immunosuppressives.
- Moderate-dose GCs (10–30 mg daily) can be used for short periods of time, for example as 'bridging therapy' while awaiting the onset of action of a slow-acting DMARD, or under special circumstances.
- Low-dose GCs (5–7.5 mg daily) can be added to DMARD therapy. Although such low GC dosages do not impart a noticeable anti-inflammatory effect, two randomized clinical trials showed that the addition of low-dose GCs to DMARDs enhances the latter's efficacy and provides some protection against radiological damage [43,44].
- GC injections: when used appropriately, intra-articular GC injections can be very effective and safe, and are used widely in rheumatologic practice (Figure 2.3). A more systematic approach using multiple intra-articular injections in early RA was recently pioneered in two clinical trials from Denmark with excellent results [45,46].

Conventional disease-modifying antirheumatic drugs

Conventional DMARDs are a heterogeneous group of pharmacological agents that were found empirically to possess antirheumatic efficacy. For most the mechanism of action is still only partially understood. The conventional DMARDs share some properties, including a slow onset of action (weeks to months, hence the older designation SAARDs), both symptom-relieving and structure-protecting efficacy and reasonable tolerability, serious potential toxicities that require monitoring through blood tests in most cases, and very low costs for these older medications. The most important DMARDs are:

- MTX widely seen as the standard first-line therapy for RA. Originally developed as a cancer therapy, this anti-metabolite

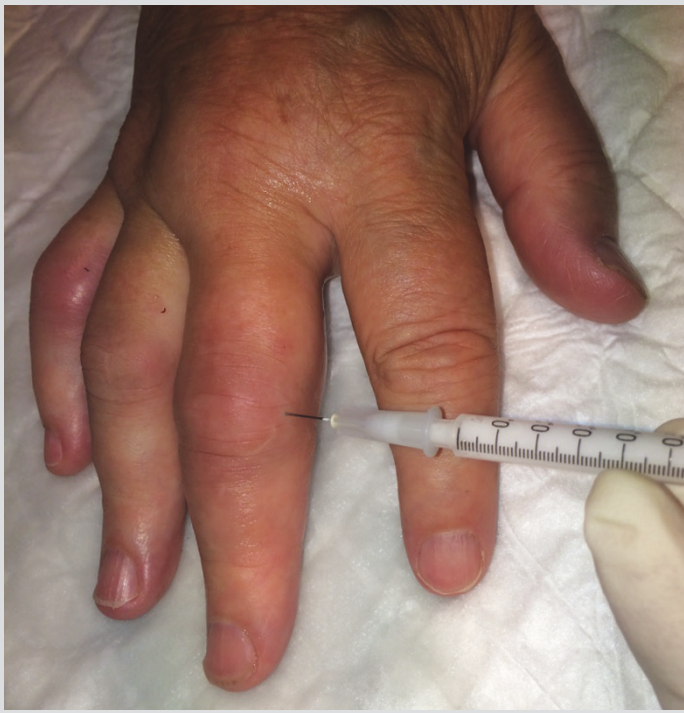

Figure 2.3 Intra-articular corticosteroid injection. The proximal interphalangeal (PIP) joint is injected. Injections of inflamed small joints can provide effective relief. Photo courtesy of Professor Bent Deleuran.

(folate antagonist) was empirically shown to have a good efficacy-to-safety profile when used at low weekly dosages for chronic diseases including psoriasis, psoriatic arthritis (PsA), and RA. In an interesting twist, later research by Cronstein et al [47] strongly suggested that it is not the anti-metabolic action of MTX that determines its efficacy in RA but rather the specific enhancement of production of the anti-inflammatory endogenous mediator adenosine [48,49]. The main risks and side effects of MTX are gastrointestinal symptoms, mouth ulcers, hepatic dysfunction, and myelosuppression. MTX is teratogenic and should never be used in patients who wish to become pregnant.

- SSZ stands tall as the only DMARD originally developed for the treatment of RA. Based on what is most probably an incorrect hypothesis – that RA is caused by inflammatory changes in the gut triggered by certain bacteria – Nanna Svartz at the Karolinska Institute in Stockholm in the 1940s designed a molecule with both antibacterial and anti-inflammatory properties (Figure 2.4). SSZ showed promise in some studies but was forgotten in post-world war turbulence and only rediscovered in the 1960s when it was proven to be very effective in inflammatory bowel disease (IBD) as well as in RA. Today, it is considered a solid alternative to MTX as first-line treatment of RA, and can also be combined with MTX to achieve greater efficacy. The main risks and side effects are allergic reactions (sulfa allergy), gastrointestinal symptoms, hepatic dysfunction, and myelosuppression.

Figure 2.4 The molecular structure of sulfasalazine. Although based on a hypothesis that is most likely not correct, the molecule that Prof Nanna Svartz constructed and that combines the anti-inflammatory effect of acetyl-salicylic acid with a sulfa-antibiotic does have efficacy in both inflammatory bowel disease and in rheumatoid arthritis. Reproduced with permission from © SVT Bild, 2015. All rights reserved. SVT Bild [52].

- HCQ, an antimalarial agent, was serendipitously found to have antirheumatic properties. It is considered a weaker agent that is rarely used as monotherapy but can be combined with MTX and SSZ in the so-called 'triple therapy' regimen pioneered by O'Dell et al [50]. HCQ is generally well-tolerated but carries a very small risk for retinopathy.
- Leflunomide, a pyrimidine synthesis antagonist, was demonstrated to be as effective as MTX [51] and has similar side effects and risks, and it is therefore often a reasonable alternative to the latter. Combining leflunomide and MTX adds efficacy but at the risk of more severe toxicity [41].

Non-pharmacological treatments for rheumatoid arthritis

In addition to these pharmacological therapies, non-pharmacological interventions are important in the overall management of patients with RA.

Physical therapy (physiotherapy) is recommended for all patients when the diagnosis is made and at many time points during the course of the disease. The aim must be to optimize the patient's condition from a functional point of view, while physical therapy can also add considerably to pain control and general well-being [53]. Physical therapy is the key ingredient of medical rehabilitation for patients with RA, a large medical need for many patients that is frequently not sufficiently integrated into the care of many patients with this disease [54].

Occupational therapy can ensure that the patient benefits from the many adjustments that can be made in daily life, both in the home and at the work place, to the limitations caused by RA.

Nutritional advice is requested by many patients. The scientific basis for providing such advice is, however, rather limited. One small randomized study showed that a diet that was both gluten-free and vegan gave some improvement to the patients but was difficult to follow [55]. Another study showed that the 'Mediterranean diet' provided distinct benefits to patients [56]. As the latter diet is generally acceptable to the patient for the long term and is also associated with significant general and cardiovascular health benefits, at this time that may be the best practical recommendation to give to a patient with RA interested in

modifying the diet. Formal contact with a nutritionist will facilitate this from a practical point of view.

Most patients will at some point or other during the course of their disease require psychosocial support. This can be provided by different means, for example through contact with a social worker or psychologist, support groups organized through hospitals, clinics, or – most often – through the patient associations. The physician's most important contribution is to recognize when the patient is in need of such intervention and to refer or facilitate contact. Needless to say, the rheumatologist can also provide a great deal of psychological support to the patient by having an empathic and understanding attitude towards the patient with a life-long serious disease.

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Chapter 3

Overview of biologic therapies

Brief historical review of the emergence of biologics for rheumatoid arthritis

The discovery of the technology for producing monoclonal antibodies by Kohler and Milstein in 1975 [1] heralded a new era in therapeutics: it became possible to design a molecule with a very specific predetermined biological effect for use in a relevant disease. Applications of the technology rapidly entered the medical fields of oncology and transplantation medicine. In rheumatoid arthritis (RA) treatment, the first attempts at biological therapy focused on T lymphocytes, with great initial excitement but subsequent disappointment as the treatments were found to be either ineffective (anti-CD4) [2,3] or too toxic for general use (anti-CD52) [4]. Meanwhile, in a parallel development in critical care medicine the use of biologic antagonists of tumor necrosis factor (TNF) were pioneered for use in septic shock. These developments also resulted in disappointment [5–8]. However, in a remarkable twist, researchers at the Kennedy Institute in London concluded that in vitro data from their studies suggested that TNF antagonism would benefit patients with RA, and they were able to convince the company that had produced one of the anti-TNF monoclonal antibodies to let them do trials with it [9]. The results exceeded all expectations and a new era in RA therapeutics was born.

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DOI 10.1007/978-3-319-13108-5_3

Overview of currently available biologic therapies

At present, nine different biologic agents are approved for the treatment of RA in the US and in Europe: five TNF-antagonists and four biologics with a different mechanism of action (Figure 3.1).

In addition, a small-molecular agent with biologic-like effects has been approved in the US (and many other countries around world), an anti-TNF biosimilar has been approved in Europe, and additional biologics are in late-stage development for RA.

The five approved TNF antagonists are summarized in Table 3.1. They differ in structure, half-life, route of administration (intravenous or subcutaneous), dose, frequency, and in some practical aspects, but they are remarkably similar in both efficacy and safety. National and international recommendations and guidance documents generally treat these medications as a single group.

The other four approved biologics are blockers of interleukin (IL)-1, IL-6, a T-cell costimulation antagonist, and a B-cell depleting agent, and these are summarized in Table 3.2. All these medications will be discussed in more detail in subsequent chapters.

Biologic versus synthetic disease modifying antirheumatic drugs: similarities and differences

The introduction of biologics into the rheumatologic armamentarium marked a dramatic shift in this therapeutic area (Box 3.1).

The approval and subsequent adoption into practice of the first two anti-TNF agents, etanercept and infliximab, was associated with enormous enthusiasm within the profession but also – as is fair to point out – marketing efforts unprecedented in the world of inflammatory diseases. On one level, the biologic medications that are used for RA can be regarded simply as disease modifying anti-rheumatic drugs (DMARDs); and indeed the designations cDMARDs and bDMARDs for conventional and biologic DMARDs, respectively, have been gaining ground. From a regulatory point of view the approval of a biologic in the treatment of RA is based on the same requirements as for conventional pharmaceuticals: clinical efficacy has to be proven in at least two randomized trials of sufficient size, and radiological efficacy in terms of

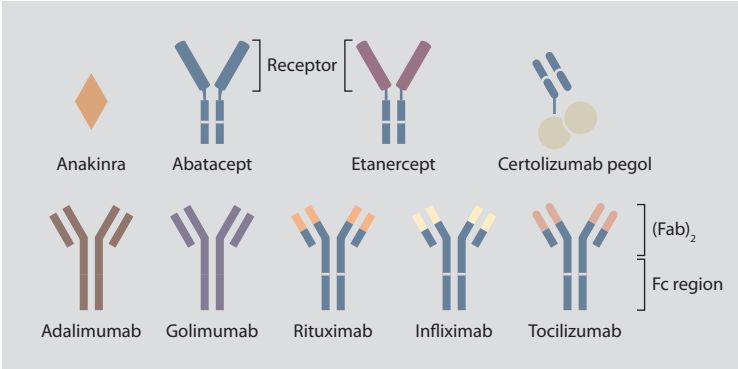

Figure 3.1 Nine biologics, with five distinct mechanisms of action, are currently approved for the treatment of rheumatoid arthritis. Many of these are approved for use in other diseases as well. Reproduced with permission from © Nature Publishing Group, 2011. All rights reserved. van Vollenhoven [10].

Brand name	Generic name	Route of administration	Usual dose	Usual starting frequency of administration
Enbrel	Etanercept	Subcutaneous	50 mg	Once a week
Remicade	Infliximab	Intravenous	3 mg/kg	Every 8 weeks
Humira	Adalimumab	Subcutaneous	40 mg	Every other week
Cimzia	Certolizumab	Subcutaneous	200 mg	Every other week
Simponi	Golimumab	Subcutaneous	50 mg	Once a month

Table 3.1 Characteristics of the five approved anti-tumor necrosis factor agents.

Brand name	Generic name	Mechanism of action	Route of administration	Usual Dose	Usual starting frequency of administration
Kineret	Anakinra	IL-1 blockade	Subcutaneous	100 mg	daily
MabThera; Rituxan	Rituximab	B-cell depletion	Intravenous	500–1000 mg	Two infusions every 6 months
Orencia	Abatacept	T-cell co-stimulation modulation	Intravenous	500–1000 mg	Every 4 weeks
			Subcutaneous	125 mg	Once a week
Actemra; Roactemra	Tocilizumab	IL-6 blockade	Intravenous	4–8 mg/kg	Every 4 weeks
			Subcutaneous	162 mg	Once a week

Table 3.2 Characteristics of the four approved biologics with mechanisms other than tumor necrosis factor blockade. IL-1/6, interleukin 1/6.

slowing down or preventing radiographic progression, improvements in physical function, and an overall satisfactory safety profile also have to be demonstrated. One might ask in which regard biologics were so much better than, or truly different from, conventional DMARDs to warrant the enormous enthusiasm and rapid and widespread uptake in practice that ensued over the decade after their initial introduction. There are several important points to make:

Box 3.1 | A Nobel Prize for anti-TNF?

Many have speculated that the discovery of anti-tumor necrosis factor (TNF) therapies for the treatment of rheumatoid arthritis (RA) and many other inflammatory diseases represents such a monumental clinical and scientific breakthrough that it should be rewarded with a Nobel Prize – but so far this has not been the case. The scientists most notably associated with the development of anti-TNF therapy in RA, Sir Ravinder Maini and Sir Marc Feldmann, did win many other world-class scientific prizes including the Lasker Award and the Crafoord Prize but the most prestigious medal from Stockholm has so far eluded them.

Box Figure 3.1 Sir Ravinda Maini and Sir Marc Feldman. Reproduced with permission from © Imperial College London, 2015. All rights reserved. Imperial College London.

1. Biologics can be effective where conventional DMARDs have failed. When the first two anti-TNFs were introduced, every practicing rheumatologist had a cadre of patients in her/his practice who had already failed every DMARD that was available. These patients had ongoing inflammatory activity, progressive destruction in the joints, a severely reduced quality of life, and a poor prognosis. Soon it became clear that many of these patients had impressive

By contrast, the person who constructed etanercept, one of the most widely used and most commercially successful biologics in the world, did win the Nobel Prize – but not for this feat. In the early 1990s Professor Bruce Beutler and his research team at the Rockefeller University constructed the molecule later designated etanercept from the naturally occurring p75 TNF receptor, as part of their research into innate immunity. For his work in that field Bruce Beutler (Box Figure 3.2) was indeed awarded the Nobel Prize in 2011 – but without reference to etanercept.

Box Figure 3.2 Professor Bruce Beutler constructed the dimerized tumor necrosis factor receptor that became the biological agent etanercept. Later he won the Nobel Prize for the discovery of Toll-like receptors. Reproduced with permission from © The University of Texas Southwestern Medical Center, 2014. All rights reserved. The University of Texas Southwestern Medical Center.

responses to the new agents and some achieved a state of disease control they had never had before. This fact alone certainly contributed greatly to the excitement surrounding the introduction of the first anti-TNFs.

2. Biologics, and specifically the anti-TNF biologics, can have a very rapid onset of action. Some patients report improvement on the same day they receive the first treatment or on the day after. Such rapidity of improvement was previously only seen with high-dose glucocorticoids (GCs), and contrasted starkly with the time to response with methotrexate (MTX) and other DMARDs, which would typically be 2–3 months or more. Needless to say, for the patients this was a stunning new development, and their enthusiasm readily spilled over to the whole profession. It is also important that the biologics having such quick effects, their effectiveness is obvious, whereas patients and physicians have always had some difficulties in knowing exactly how much the conventional agents were helping. Clinical trials is one thing, personal experience another.
3. Soon after their approval, the first results were published on radiographic efficacy of the anti-TNF agents. In this regard, they exceeded expectations. The degree of slowing down of the radiological progression was even greater than had been expected and led to widespread excitement about the possibility of preventing future joint damage almost completely.
4. Anti-TNF agents, and biologics in general, are surprisingly well-tolerated and relatively safe. For some, it was counterintuitive that a chronic disease such as RA would be treated with parenteral medications, and patient acceptance of such treatments was hard to predict. However, it rapidly became clear that as long as the patients perceived good efficacy they had no problem with infusions or injections (except perhaps with the daily injections of anakinra that came several years later; more on this agent in chapter 4). There were also major concerns about various potential long-term consequences of blocking specific cytokines, severe infections and malignancies being among the major ones cited. Indeed, some of these concerns did materialize, for example, when

it became clear that anti-TNF therapies can lead to reactivation of latent tuberculosis, or when the risk for some skin cancers was reported to be increased; but on balance, the absolute risks associated with anti-TNF treatment were found to be small and manageable, and they certainly compared favorably with those seen with conventional DMARDs.

5. Biologics have a well-defined and specific mechanism of action (Figure 3.2). In stark contrast to the conventional DMARDs, whose mechanisms of action are only partially understood and which invariably have many different biologic effects that may or may not be clinically relevant, the biologics target a single molecule or cell-type and therefore every observed effect must be related to that cause.

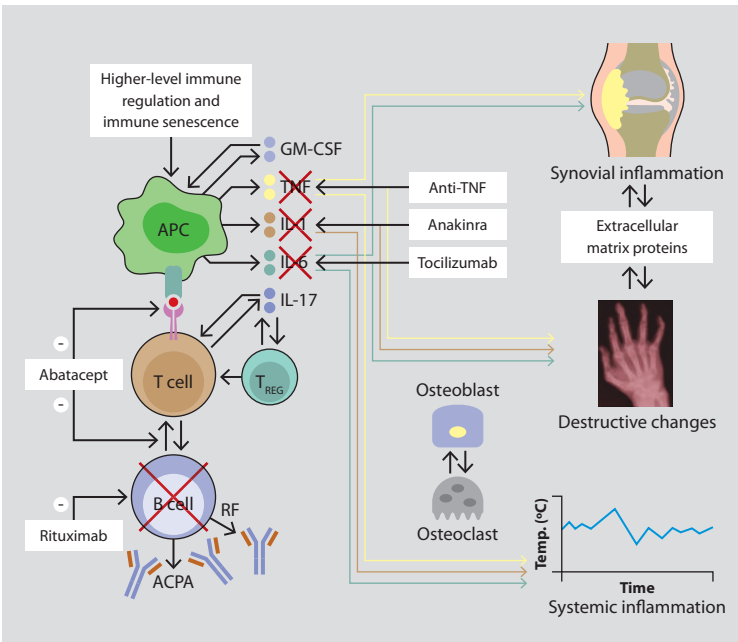

Figure 3.2 The mechanism of action of the various biologics are highly specific and known: the figure illustrates at exactly which point the biologic intervenes in the inflammatory cascade – something that would be impossible to do for the conventional antirheumatic agents. ACPA, anti-citrullinated protein antibody; APC, activated protein C; GM–CSF, granulocyte macrophage–colony stimulating factor; IL-1/6/17, interleukin 1/6/17; RF, rheumatoid factor; TNF, tumor necrosis factor; TREG, regulatory T cells. Reproduced with permission from © Nature Publishing Group, 2009. All rights reserved. van Vollenhoven [11].

Current guidelines for biologic use in rheumatoid arthritis

The use of biologics for RA is regulated and directed at many different levels. Regulatory bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) grant approval for the use of these agents, specifying the indication and usually some additional constraints. However, because the latter are based on Phase III clinical trials they are often not very relevant for clinical practice, being either too general to be useful ('approved for patients with active disease') or too vague ('having failed other therapies'). Thus, many professional organizations have published guidelines on the use of biologics, and these have also been revised on several occasions. Moreover, health care payers are increasingly determining the uses of medications that can be reimbursed. In some countries, national organizations have been established to determine if a medication that has been approved from a regulatory point of view will also be reimbursed by the (national) health insurance system. Pharmaceutical companies have been understandably critical of having to pass two separate tests for the same new drug. The most important guidelines pertaining to the use of biologics in RA are:

- The American College of Rheumatology (ACR) 2008 recommendations for the use of non-biologic and biologic DMARDs in RA [12]. According to these, the first-line treatment of RA is MTX or another conventional DMARD. In patients with early RA who have moderate or high disease activity despite such treatment biologics can be used. Distinctions are made for patients with early versus established RA and those with or without markers for a poorer prognosis, but the biologics are by-and-large considered as equivalent. The ACR recommendations have recently been the subject of a thorough revision but no major changes are anticipated.
- The European League Against Rheumatism (EULAR) recommendations for the management of RA with synthetic and biologic DMARDs. These recommendations were originally published in 2010 [13] and updated in 2013 [14]. The original document recommended MTX as the first-line treatment for RA,

but suggested that in some patients with severe disease and poor prognostic markers the early use of biologics could be considered. The 2013 update eliminated the latter possibility, probably because of uncertainty on how best to identify such patients. The updated recommendations also support the use of combinations of conventional DMARDs before going to biologics.

- The National Institute of Clinical Excellence (NICE) in the United Kingdom is the largest national-level payer organization in the world and has its own rules for reimbursing biologics for RA. Some notable differences from the professional guidelines described above are that biologics are reimbursed only when used for patients with high disease activity as documented by a Disease Activity Score (DAS)28>5.1; that more conventional DMARDs have to be failed before starting biologics; and that only a limited number of biologics can be tried in each patient.

When reading guidelines and recommendations such as these, it is important to recognize that they typically are the result of long, protracted efforts by large groups of individuals – usually having representation from several relevant professions as well as patients – followed by a lengthy time of further refinements and the publication process, and that they therefore by necessity tend to 'lag behind' scientific developments in the field by a considerable margin. Likewise, the authors must consider many different potential uses of their recommendations: while intended primarily for practicing rheumatologists, they will without doubt be used by the pharmaceutical industry in order to promote the use of medications at a higher cost, whereas administrators and payers will try to use the recommendations to steer therapies towards lower-priced alternatives and cost containment. Politicians and patient organizations are also going to use these kinds of recommendation to their best advantage. Faced with such complexities, it is perhaps not surprising that these large multinational guidelines and recommendations often tend to be somewhat bland and lacking in specifics. National guidelines and those at the regional or local level may sometimes have more specifics and be of greater help to the individual practitioner.

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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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DOI 10.1007/978-3-319-13108-5_4

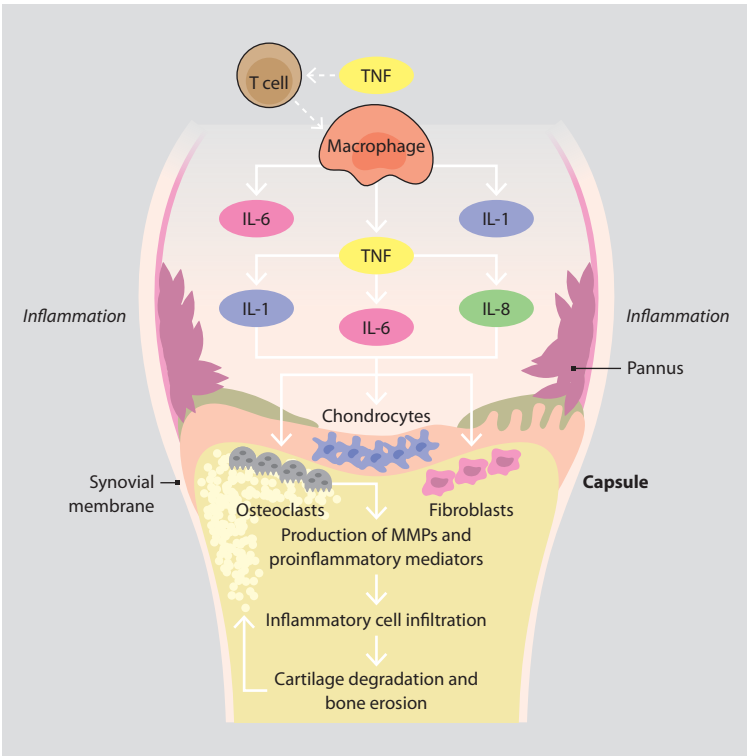

Figure 4.1 The pathophysiology of rheumatoid arthritis depicted as a cascade, in which tumor necrosis factor (TNF) is upstream from interleukin (IL)-1, IL-6, and IL-8. MMP, matrix metalloproteinases.

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.

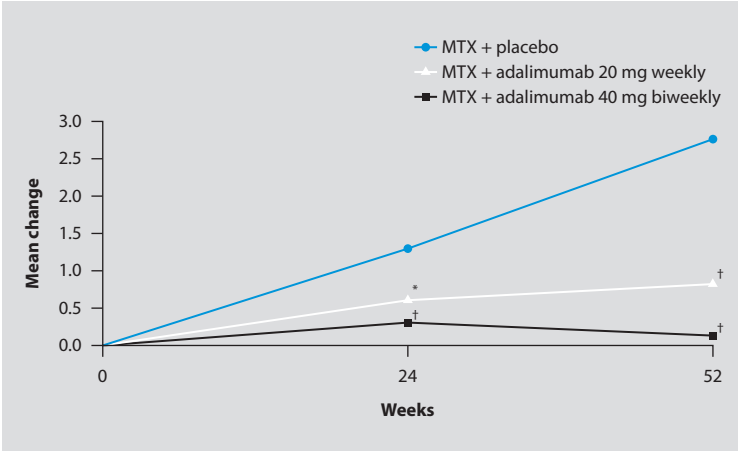

Figure 4.2 The radiological efficacy of adalimumab was demonstrated in the trial by Keystone et al. While patients on MTX plus placebo have a clear linear radiological progression (open circles), the combination of MTX and the anti-TNF agent almost completely abolishes this (closed triangles, 20 mg weekly; 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

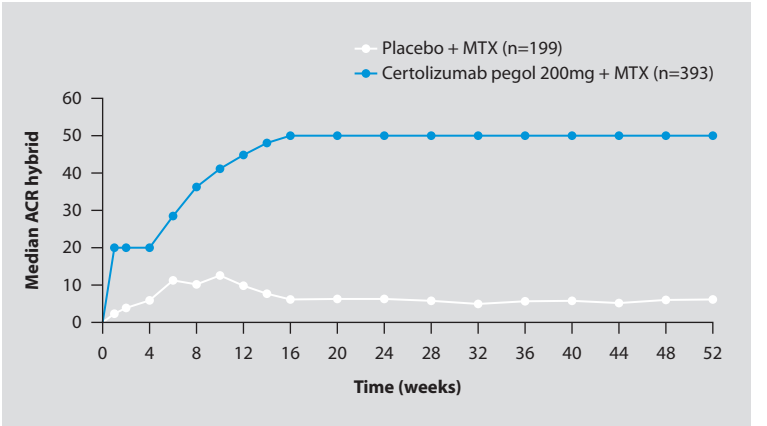

Figure 4.3 The efficacy of certolizumab pegol as reanalyzed using the American College of Rheumatology-hybrid outcome. Clear separation between active treatment and placebo is seen. ACR, American College of Rheumatology; MTX, methotrexate. Reproduced with permission from © John Wiley and Sons, 2011.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

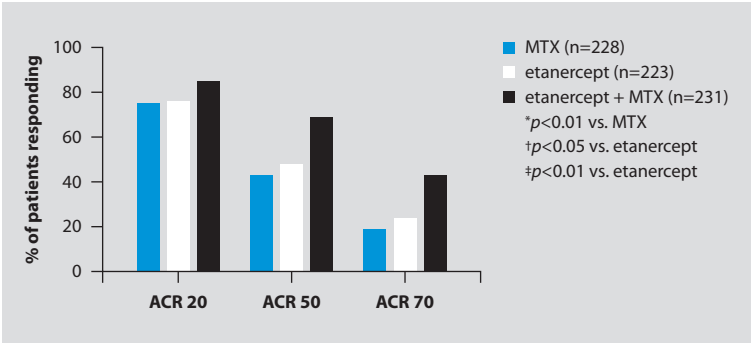

Figure 4.4 Efficacy of etanercept in methotrexate-naive patients with rheumatoid arthritis. The clinical outcomes with the combination of MTX plus etanercept are significantly superior to either monotherapy, and the difference is most notable for the 'high-end' outcomes such as ACR70. ACR, American College 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).

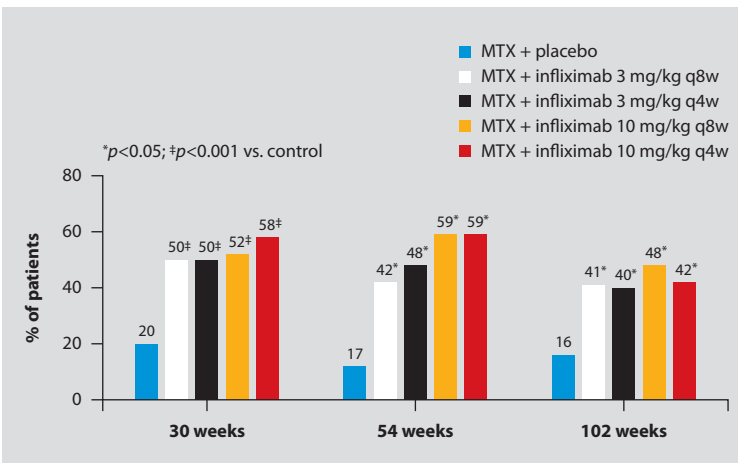

Figure 4.5 Results from the Attract trial demonstrated the efficacy of infliximab in patients with an inadequate response to methotrexate. The results were accepted by both the US FDA and the EMA (then: EMEA) as sufficient for granting approval. MTX, methotrexate. Adapted from © Massachusetts Medical 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.

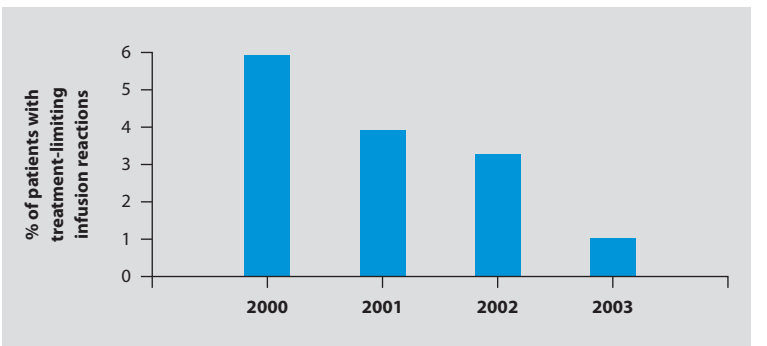

Figure 4.6 The frequency of severe infusion reactions to infliximab showed a striking decline during the first five years of use of this agent. Reproduced with permission from © BMJ Publishing Group & European League Against Rheumatism, 2007. All rights reserved. Augustsson et al [44].

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

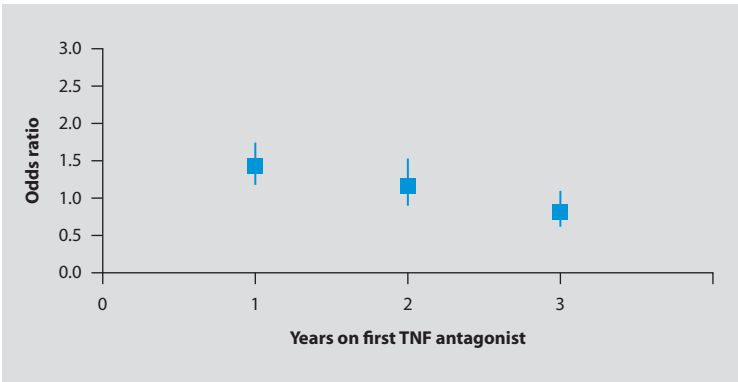

Figure 4.7 Risk for infection requiring hospitalization during the first three years of anti-TNF treatment in the Swedish national biologics registry Anti-Rheumatic Therapy In Sweden (ARTIS). TNF, tumor necrosis factor. Reproduced with permission from © BMJ Publishing Group & European League Against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

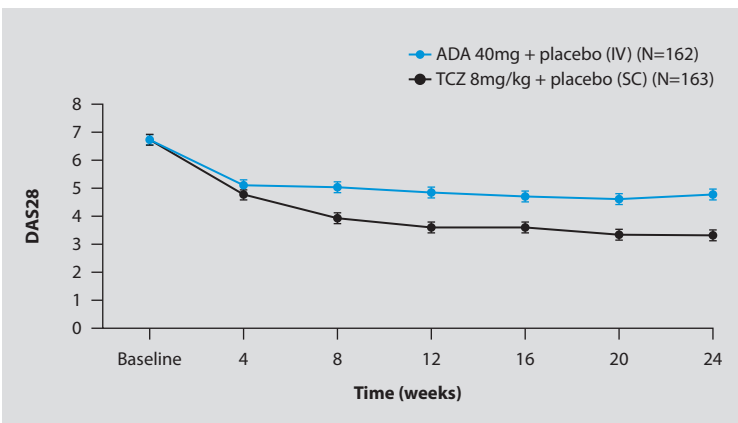

Figure 4.8 The Adacta trial demonstrated that the interleukin-6 antagonist tocilizumab as monotherapy was superior to adalimumab as monotherapy. Adapted from © Elsevier, 2013. All rights reserved. Gabay et al [61].

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

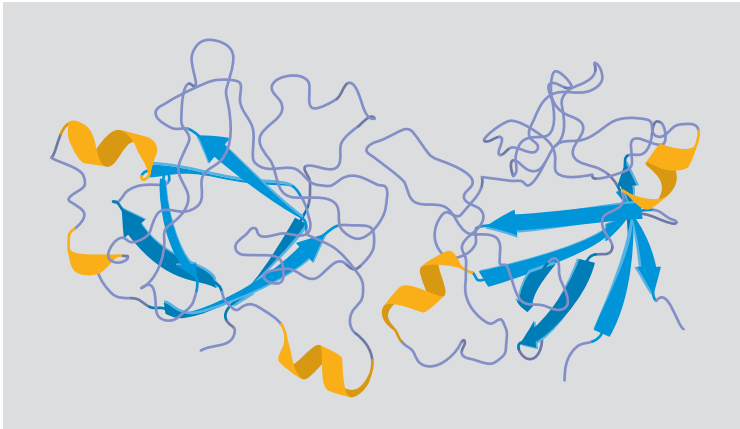

Figure 4.9 The structure of the interleukin 1 receptor antagonist (IL-1RA), a naturally occurring antagonist of IL-1. It was cloned to become the biologic treatment anakinra.

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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Chapter 5

B-cell directed therapy

Introduction

Appreciation of the role of B-lymphocytes in the pathogenesis of rheumatoid arthritis (RA) has gone through various cycles. The discovery of rheumatoid factors as a specific marker for the disease pointed to a possible role for humoral (antibody-mediated) immunity and this was further strengthened by the discovery of anti-citrullinated peptide antibodies (ACPAs) many decades later [1,2]. However, animal model research in the 1970s and 1980s strongly supported the view that RA-like inflammation could be induced almost exclusively through T-cell-mediated immunity, and the first biologics to be tested in RA were directed against the T lymphocytes, albeit with mixed success. The subsequent successes with anti-tumor necrosis factor (TNF) approaches emphasized the importance of macrophage-like cells in RA inflammation, and a commonly held view was that B cells only played a very minor role in this disease. Despite all this, Professor Jonathan Edwards in London remained convinced that B cells were of greater importance in RA and published a hypothesis suggesting rheumatoid factor of the immunglobuin G (IgG) isotype could form small immune complexes that would specifically trigger inflammation in the target tissues of RA (Figure 5.1) [3].

Based on this model he proposed that a strongly B-cell depleting therapy would break the vicious cycle of RA inflammation, and he initiated a small uncontrolled treatment trial where corticosteroids and cyclophosphamide were combined with the then relatively new lymphoma therapy rituximab. In the first case series several remarkable improvements were

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DOI 10.1007/978-3-319-13108-5_5

Figure 5.1 Professor Jonathan Edwards proposed that IgG-rheumatoid factors play a central role in the pathophysiology of rheumatoid arthritis and hypothesized that B-cell depletion would be effective. Based on this theory, and against prevailing dogma at the time, he initiated the first clinical trial with the B-cell depleting agent rituximab. Reproduced with permission from © J Edwards, 2015. All rights reserved [4].

noted and a more formal drug development program was initiated [5]. These and subsequent trials firmly established that B-cell depletion can be an effective therapeutic principle in RA.

Overview of B-cell therapy for rheumatoid arthritis

Rituximab

Introduction

Rituximab (Mabthera, Rituxan) is a chimeric monoclonal antibody directed against the CD20 molecule, which is present on all mature B cells. On binding to CD20, rituximab triggers cells death through antibody-mediated cellular cytotoxicity; following infusion of rituximab complete depletion of B cells from the peripheral blood can be documented within a matter of days. This monoclonal antibody was originally approved for the treatment of non-Hodgkin lymphoma and became one of the most widely used biologics in hematology. Since its original development in the field of hematology it has been used 'off-label' for the treatment of many autoimmune diseases and studied formally in some of these; it has been approved for the treatment of **a**nti-**n**eutrophil **c**ytoplasmic **a**utoantibody (ANCA)-associated vasculitis [6,7] and there are many studies suggesting efficacy in at least some patients with systemic lupus erythematosus (SLE) [8] and multiple sclerosis [9].

Rituximab efficacy

The first randomized trial with rituximab in RA demonstrated excellent efficacy when given either as monotherapy or in combination with MTX or even with cyclophosphamide [10]. The combined therapies provided a more prolonged benefit and subsequent trials were invariably done on a MTX background. These trials included patients who had failed treatment with at least MTX but in most cases also with at least one anti-TNF agent, and responses were numerically comparable to those seen in anti-TNF trials [11,12]. Rituximab was also shown to slow radiologic progression [13]. Despite the rapid biologic effect of the treatment (B-cell depletion occurring in a matter of hours or days) the onset of clinical action was somewhat slower. A later randomized trial was done in patients with RA who had not previously been treated with MTX and who therefore mostly had early RA. This study demonstrated that rituximab in combination with MTX was more effective, both clinically and radiographically, than MTX alone (Figure 5.2) [14].

Rituximab safety

Treatment with rituximab in hematology was associated with a rather high frequency of infusion-related reactions including some that were severe or even life-threatening, having their origins in the massive lysis of malignant lymphocytes. Thus, considerable caution was exerted in the treatment of RA but it became clear that although infusion reactions were certainly seen they were much less frequent and rarely severe. Nevertheless, premedication with glucocorticoids (GCs) is recommended with rituximab infusions and the infusion site has to be equipped to deal with severe reactions. Also, a delayed infusion reaction, occurring 7–14 days after infusion and resembling 'serum sickness' has been seen in some patients. Other adverse events are uncommon. In controlled trials, the frequency of infections following rituximab was not markedly elevated, and long-term follow-up of patients in clinical trial extension programs has not revealed any unexpected safety concerns [15]. Patients who are treated with rituximab on a continuous basis do have more or less persistent B-cell depletion (at least in the peripheral blood). Not surprisingly, decreasing levels of IgM occur quite frequently, and

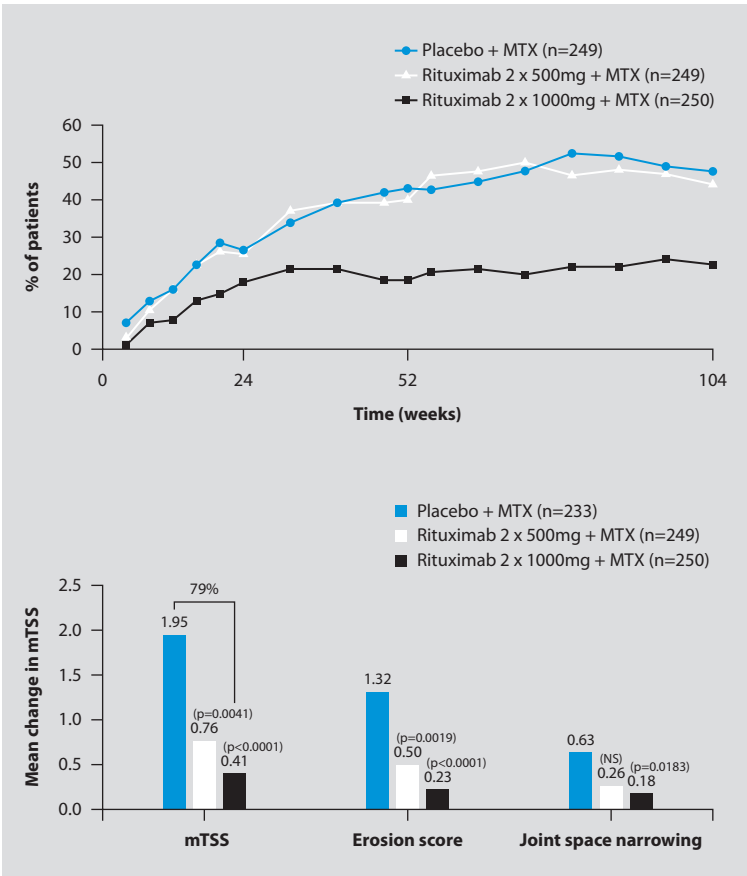

Figure 5.2 Rituximab was studied in patients with rheumatoid arthritis who had not previously been treated with methotrexate. (A) The combination of rituximab with MTX was superior both clinically (above; shown is the EULAR good response); (B) and radiographically (below). However, note that rituximab is not approved for use in this setting. EULAR, European League Against Rheumatism; MTX, methotrexate. Reproduced with permission from © BMJ Publishing Group Ltd, 2012. All rights reserved. Tak et al [14].

low IgG is seen in some. Further studies have suggested that while low IgM is not associated with an increased risk for infection, low IgG levels might be. In post-marketing surveillance and spontaneous reporting a small number of cases of progressive multifocal leukoencephalopathy (PML) have emerged [16]. This reactivation of the John Cunningham virus in the central nervous system leads to a severe and frequently fatal

neurological syndrome, and is mostly seen in severely immunocompromized patients. Extensive analyses have been completed to determine whether an increased risk is indeed associated with rituximab and this has not yet been resolved [17]. Even if there is an increased risk, the absolute risk remains very small – approximately one in 20,000 patients.

Rituximab use

Rituximab is approved for use in patients with RA who have previously failed anti-TNF therapy, although in practice it is also used in patients where anti-TNF is considered less desirable [18]. The approved dosage is 1000 mg given intravenously twice with two weeks in between; this 'course' can then be repeated. In practice, repeat courses are often given when disease activity recurs, but some studies suggest that it is advantageous to schedule 6-monthly repeat courses as a standing order. There is some uncertainty regarding the optimal dosing since the Phase III trial program in effect only tested one dosage. Both randomized trials and observational studies strongly suggest that a course consisting of 500 mg given twice, or possibly 1000 mg given once, is just as effective as the approved dosage (Figure 5.3) [11,19,20]. The pharmacoeconomic benefit of using the lower dose is obvious.

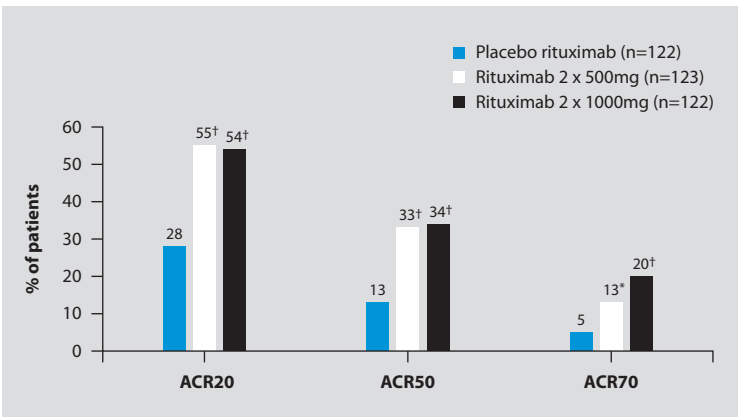

Figure 5.3 Several trials suggest that the approved dose of rituximab, 1000 mg given twice, is not better than 500 mg given twice. Data shown are from the 'Dancer' trial. The doses yield similar ACR20 (left) and ACR50 (middle) responses, while the ACR70 (right) responses show a small and statistically non-significant difference. ACR, American College of Rheumatology. Reproduced with permission from © John Wiley and Sons, 2006. All rights reserved. Emery et al [11].

Rituximab is usually given on a MTX background but has also been used as monotherapy or in combination with other disease-modifying antirheumatic drugs (DMARDs). Although the monotherapy seems slightly less effective, one large observational study suggested that the combination of rituximab with leflunomide may be even more effective than the MTX combination [18].

Other B-cell targeting biologic therapies

Other B-cell depleting therapies

Several other B-cell directed biologics have been developed over the years, but none are currently approved for the treatment of RA. The anti-CD20 monoclonal antibody ocrelizumab was studied in Phase II/III trials for RA but severe infections led to termination of the trial program [21–23]. The fully human anti-CD20 monoclonal antibody ofatumumab (Arzerra) is approved for the treatment of chronic lymphocytic leukemia and has been tested in RA [24–26]. Results in the trials were favorable and it seems that the program was terminated mostly for business reasons.

Non-depleting B-cell targeted therapies

Epratuzumab is an anti-CD22 monoclonal antibody that does not deplete B cells but instead downregulates their activity and is currently being tested for the treatment of SLE [27] but not for RA. Several biologics have been developed that target BAFF/Blys, the B-cell stimulating cytokine. Belimumab had only modest effects in RA [28] but was approved for the treatment of SLE. Tabalumab also had modest efficacy in RA [29,30] but is not being developed further. The development programs of two other Blys-antagonists, atacicept and blisibimod, have been directed at treating SLE rather than at RA.

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Chapter 6

T-cell directed therapy

Overview of T-cell directed therapy for rheumatoid arthritis

The role of the T lymphocyte in the pathophysiology of rheumatoid arthritis (RA) remains somewhat unclear. On the one hand, T cells are abundantly present in the inflamed synovium, and in some animal models T cells can be identified as the main effector cells of the inflammatory response. Moreover, the demonstration that human leukocyte antigen (HLA)-DR genotypes are associated with the risk for RA points at the T cell, because the function of the class II major histocompatibility complex (MHC) molecule in the immune response is exerted through binding to the T-cell receptor. On the other hand, it was demonstrated that the human rheumatoid synovium does not present abundant evidence for T-cell activation, and cyclosporin-A, the one conventional antirheumatic agent that is believed to work almost exclusively through inhibition of T cells, has only limited efficacy in RA. Nonetheless, the first biologics to be tested for RA were directed at T lymphocytes. Approaches using anti-CD4 (targeting T-helper [Th] cells) were ineffective [1] and although alemtuzumab (Campath-1H), an anti-CD52 monoclonal that targets all T cells, did demonstrate efficacy in RA [2], it is thought to be too toxic for general use in this condition. Currently, the only successful approach directed at T lymphocytes is through targeting co-stimulation.

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DOI 10.1007/978-3-319-13108-5_6

Abatacept

The T-cell directed biologic abatacept (Orencia) has demonstrated efficacy in RA and is an approved treatment in this setting. Abatacept is a construct of the naturally occurring cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) coupled to an immunoglobulin G (IgG) framework. CTLA-4 is produced by T cells around 48 hours after activation and it interferes with the binding of the CD28 molecule on the T-cell surface and the CD80/86 (B7) molecule, which is present on antigen-presenting cells. The latter interaction is a 'second signal' that enhances the T-cell response, and therefore blocking it serves to downregulate T cells. The physiologic role of CTLA-4 is believed to be the termination of T-cell activation and the prevention of excessive inflammation. The development of this molecule as a therapeutic agent was therefore a logical step, and indeed, several trials confirmed that abatacept has good clinical efficacy in the treatment of RA in different stages of the disease [3]. Efficacy that was comparable to anti-tumor necrosis factor (TNF) was demonstrated in patients who had an incomplete response to methotrexate (MTX) [3], and good clinical efficacy was also demonstrated in patients who had previously failed anti-TNF [4] (Figure 6.1).

Abatacept was also shown to inhibit radiologic progression [6,7] and to be effective in patients with early RA [8], even in those with early undifferentiated arthritis [9]. Perhaps most impressively, a head-to-head comparison with adalimumab, when both were given in combination with MTX, showed almost identical efficacy for the two agents [10]: the percentages of responders according to the American College of Rheumatology (ACR) criteria were virtually identical at all time points and the time to response for the two drugs was also almost identical. The recent Avert trial in early RA confirmed that abatacept plus MTX was more effective in early RA than either drug alone [11].

The safety profile of abatacept in clinical trials was favorable. Small increases of infections and other minor adverse events were observed, as was the case with all immunomodulatory agents, but this treatment does not seem to be associated with major risks. Screening for tuberculosis is recommended but an increased risk for reactivation of latent tuberculosis has not been demonstrated.

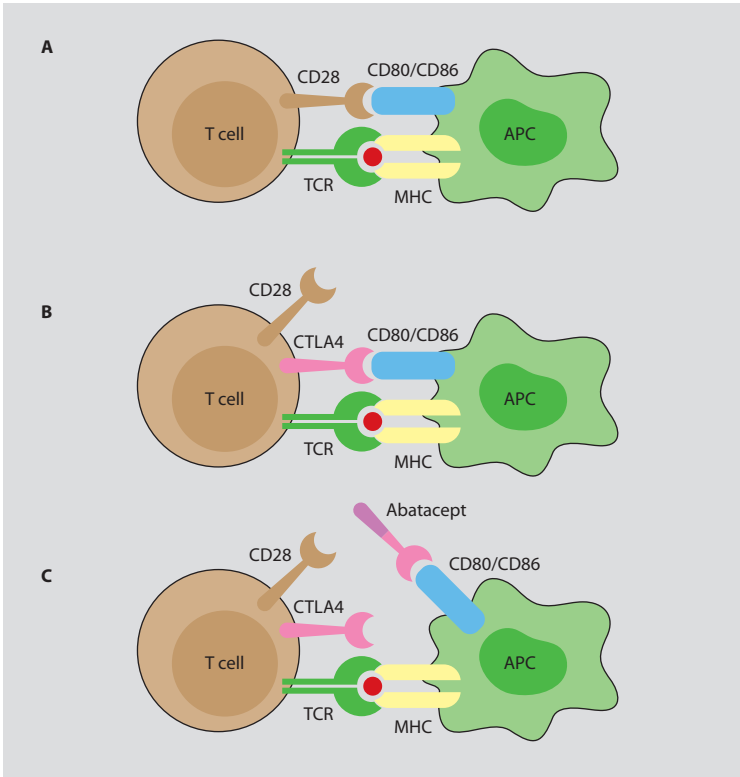

Figure 6.1 The mechanism of action of abatacept. T-cell activation is initiated by binding of the TCR to an antigenic peptide presented by the class I or II MHC molecule on the surface of an APC. However, for activation to result, a second signal is needed, and one of the possibilities for this is the binding of CD28 on the T-cell surface to CD80/86 on the surface of the APC (A). After 24–48 hours, the activated T cell begins expressing the molecule CTLA4, which has a higher affinity for CD80/86 than CD28. This molecule will then disrupt the CD28-CD80/86 binding and terminate T-cell activation (B). Abatacept is a dimeric construct of the CTLA4 molecule and strongly binds CD80/86, thereby preventing or interfering with T-cell activation (C). APC, activated protein C; MHC, major histocompatibility complex; TCR, T-cell receptor; Reproduced with permission from ©Nature Publishing Group, 2006. All rights reserved. Ruderman and Pope [5].

Abatacept can be used as monotherapy or combined with MTX or other disease modifying antirheumatic drugs (DMARDs). A single trial using the combination of abatacept with the anti-TNF agent etanercept had a high rate of severe infections and this combination is considered contraindicated [12].

The initial approval for abatacept was as an intravenous infusion at a dosage of 500, 750, or 1000 mg based on body weight, given every 4 weeks. A subcutaneous version was later approved at 125 mg weekly. The two forms of administration have formally been shown to be equivalent in terms of efficacy [13] and choosing between them is mostly a matter of preference.

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Chapter 7

Novel biologics and small molecules with biologic-like effects

Introduction

Dozens of cytokines are involved in the inflammatory process and it stands to reason that many of them could be targeted successfully in the treatment of inflammatory diseases. Translational researchers have extensively surveyed this field over the past decades and several potential targets for therapy have emerged (Figure 7.1). Some have fallen by the wayside, but others are now progressing through advanced clinical testing and two have already reached the clinic in some parts of the world, albeit for indications other than rheumatoid arthritis (RA).

Novel biologics

Interleukin-12/23 antagonist

Ustekinumab

Ustekinumab is an interleukin (IL)-12/23 antagonist. As IL-12 and IL-23 share a common chain (ie, each molecule consists of two chains and one of those two is the same for the two molecules) they can be targeted by a single monoclonal antibody. Ustekinumab was tested in various autoimmune diseases and was approved for psoriasis after Phase III trials showed positive results in this skin disease [2]. Ustekinumab is currently used in patients with psoriasis who are in need of systemic therapy, usually in those who have already failed methotrexate and/or an anti-tumor necrosis factor (TNF) biologic. A comparative trial suggested that it might be more effective than etanercept (given at the high psoriasis dose

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DOI 10.1007/978-3-319-13108-5_7

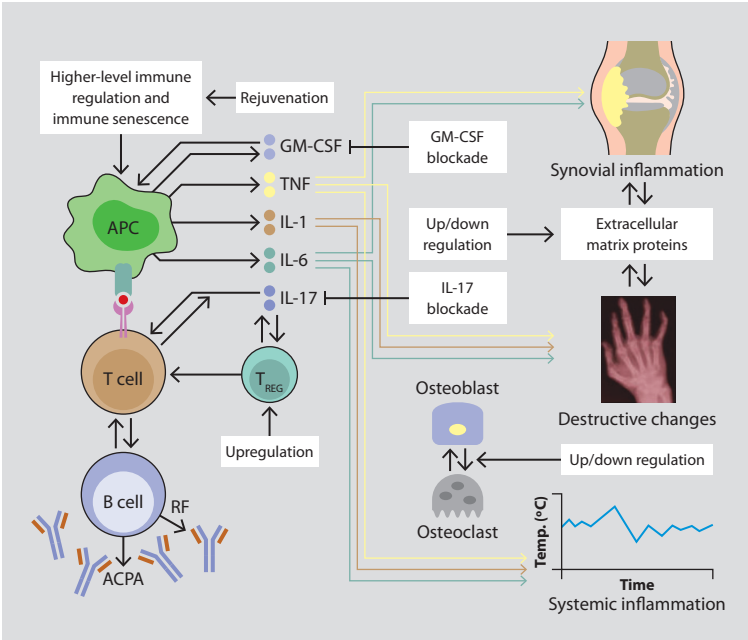


Figure 7.1 Various new approached may be considered to control the inflammatory process in rheumatoid arthritis. ACPA, anti-citrullinated protein antibody; APC, activated protein C; GM–CSF, granulocyte macrophage–colony stimulating factor; IL-1/6/17, interleukin 1/6/17; RF, rheumatoid factor; TNF, tumor necrosis factor; TREG, regulatory T cells. Reproduced with permission from © Nature Publishing Group, 2009. All rights reserved. van Vollenhoven [1].

of 50 mg twice weekly) [3]. More recently, ustekinumab has also been approved for the treatment of psoriatic arthritis (PsA) on the strength of trials demonstrating efficacy over placebo [4–6]. The absolute magnitude of the responses in these trials may be somewhat less than those seen with anti-TNF biologics, but no direct comparisons are available. There are no published trials of ustekinumab in RA and the drug is not being developed for that indication.

Interleukin-17 antagonists

Secukinumab, ixekizumab, and brodalumab

Over the past decade, important inflammatory pathways involving IL-17, IL-23 and the specific T-helper (Th)17 lymphocyte have been elucidated. Based on the biology involved, an important role for this pathway in

psoriasis has been postulated and confirmed, and clinical trials have demonstrated the efficacy of the IL-17 antagonists secukinumab [7], ixekizumab [8], and brodalumab in this setting [9–11]. Trials in rheumatologic indications have mostly focused on PsA and spondyloarthropathies but some trials have been conducted in RA.

Secukinumab binds to IL-17A and neutralizes its activity. Clinical trials have demonstrated efficacy in psoriasis [7], PsA [12] and ankylosing spondylitis (AS) [13] and the drug has been approved for use in psoriasis. A Phase II trial in RA using a range of dosages did not achieve its primary endpoint, although modest efficacy over placebo was seen for several outcomes [14]. Secukinumab is actively being studied in PsA and AS but not currently in RA.

Ixekizumab binds to and neutralizes both IL-17A and IL-17F. Trials showed efficacy in psoriasis [8]. A small Phase I and a larger Phase II trial suggested moderate efficacy in RA [15,16], but current development is in PsA and AS.

Brodalumab targets the IL-17 receptor A and showed efficacy in trials in psoriasis [9,10,17] and PsA [18]. In RA, one small trial did not suggest efficacy [19], and it is not being developed for RA. Recently, all development of brodalumab was halted.

Thus, these three novel agents that target the IL-17 pathway appear to have efficacy in psoriasis and the seronegative arthritides, with mixed results in RA trials to date. Their development programs are not directed at RA, but as these drugs are already available clinically or are likely to become so in the future, it can be hoped that more data will emerge addressing the possibility that they might benefit some patients with RA as well.

Granulocyte-macrophage colony-stimulating factor antagonist

Mavrilimumab

The monoclonal antibody mavrilimumab targets the granulocyte-macrophage colony-stimulating factor (GM-CSF), which in addition to its role in hematopoiesis has important immunoregulatory functions. The monoclonal showed convincing efficacy and good tolerability in a large Phase II trial in RA [20], and further development in phase III is anticipated.

Novel synthetic antirheumatic medications with biologic-like properties

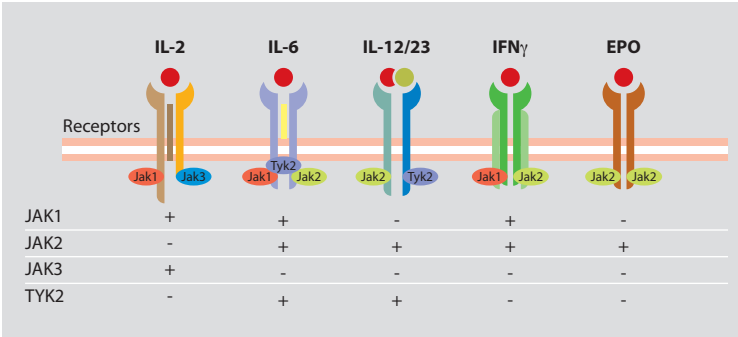
In recent years, several pharmaceutical companies have begun the development of novel small molecular agents for RA. These are by definition not biological medications, but their inclusion in this chapter is warranted on account of several considerations. Most importantly, while the distinction between conventional DMARDs and biologicals (biologic DMARDs) is based on their structure, from a clinical point of view the main characteristics of biologicals and the ones that distinguish them from conventional agents are their specifically targeted mechanism, their rapid onset of action, and their superior clinical and/or structure-protective effects. With regards to these characteristics, it has been demonstrated that at least some of the novel small-molecular antirheumatic agents do have the profile given above for biologics, and they are therefore sometimes referred to as having 'biologic-like efficacy'.

Janus kinase inhibitors

Since the first outstanding results with biologics were reported it has been speculated that small-molecular agents could be developed with the same effects. Unfortunately, years of pharmacologic development led to many failures in this regard, the development of p38 mitogen-activated protein (MAP) kinase inhibitors being an example [21]. However, the development of small-molecule agents that target the Janus kinases (JAKs) and perhaps some other intracellular enzymes has opened a new chapter in biologic therapeutics with small-molecule medications, the efficacy of which is comparable to biologics.

The JAKs are a small group of four different intracellular enzymes that belong to the large family of tyrosine kinases and that are intimately involved in the cellular activation that occurs after any of a large number of cytokines binds to its receptor on the cell surface (Figure 7.2).

Several inhibitors of JAKs have been developed as potential treatments for RA; currently one is approved while several others are in clinical development.



	IL-2	IL-6	IL-12/23	IFNγ	EPO
JAK1	+	+	-	+	-
JAK2	-	+	+	+	+
JAK3	+	-	-	-	-
TYK2	-	+	+	-	-

Figure 7.2 The Janus kinases. The Janus kinases are four intracellular enzymes that combine in various ways to mediate an activating signal from the cell membrane to the nucleus in response to binding of various cytokines to their receptors. EPO, erythropoietin; IFN γ, interferon γ; IL-2/6/12/23, interleukin 2/6/12/23; JAK1/2/3, Janus kinase 1/2/3; TYK2, tyrosine kinase 2. Reproduced with permission from © Wolters Kluwer Health, Inc., 2013. All rights reserved. van Vollenhoven [22].

Tofacitinib

Tofacitinib selectively blocks JAK1 and JAK3 and leads to decreased intracellular activation on binding to many cytokines including interferons and IL-2/4/6/15/21/12/23. In a very large Phase III clinical trial program it was shown to be clinically efficacious for the treatment of RA both in combination with methotrexate (MTX) [23,24] and other disease modifying antirheumatic drugs (DMARDs) [25], and as monotherapy [26]. Efficacy was shown to be rapid and reach levels of responses that were similar to those seen with anti-tumor necrosis factor (TNF) (Figure 7.3) [23].

Similar results were seen with the two dosages that were tested: 5 mg and 10 mg twice daily. Radiological efficacy, ie, the retardation of radiologic progression, was also demonstrated for the higher dose but in the case of the lower dosage the numerical difference that was seen did not achieve statistical significance in that trial [24]. However, a subsequent large clinical trial in patients who had not previously been treated with MTX did demonstrate that tofacitinib given as monotherapy was superior to MTX both in terms of clinical outcomes and also in preventing radiologic progression [27]. Therefore, the overall conclusion that emerges from the totality of the Phase III program is that tofacitinib is as effective as anti-TNF biologics both clinically and radiologically.

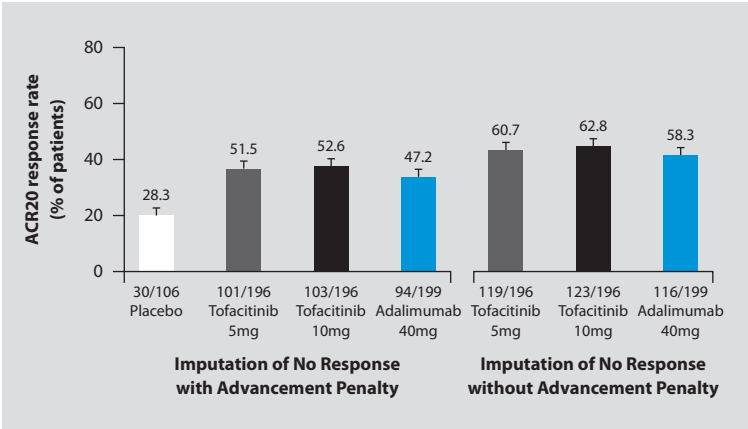


Figure 7.3 In the 'Oral-Standard' trial, the efficacy of tofacitinib was shown to be superior to placebo and numerically comparable to that of the anti-tumor necrosis factor agent adalimumab. Reproduced with permission from © Massachusetts Medical Society, *New England Journal of Medicine*, 2012. All rights reserved. van Vollenhoven et al [23].

The safety and tolerability of tofacitinib is similar to biologics in some ways but different in others. Thus, tofacitinib is generally tolerated well and the rates of adverse events in clinical trials were acceptable. A slight increase in overall infections was seen over placebo, but more importantly there was an increase in serious infections even though the absolute rate remained low. The occurrence of herpes zoster was consistently increased in the clinical trials. There were no specific signals for malignancies.

Tofacitinib treatment was associated with various laboratory abnormalities that are remarkably reminiscent of those seen with the IL-6 inhibitor tocilizumab. Hepatic transaminase elevations were seen in almost one fourth of patients and were sometimes severe. Similarly, cytopenias were seen frequently and sometimes reached high levels. These laboratory abnormalities did not, however, lead to major events, and while this is reassuring it should be emphasized that this is almost certainly due to the fact that the patients were monitored closely and that laboratory abnormalities led to protocol-specified actions on the part of the investigators to minimize risks.

In the RA trials, tofacitinib was associated with a small but consistent increase in creatinine, the cause of which is not clear. Tofacitinib

also predictably results in increases in cholesterol, both low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The long-term consequences of this are unknown.

Tofacitinib was approved by the US Food and Drug Administration (FDA) and by most other drug authorities in the world, but not by the European Medicines Agency (EMA). The US approval is for the 5 mg dose orally twice daily, and it can be used as monotherapy or in combination with MTX or other DMARDs.

Other JAK inhibitors in development for rheumatoid arthritis

Baricitinib is a JAK antagonist with specificity for JAK1 and JAK2. In a Phase II trial it has shown very good efficacy, comparable to biologics and with Tofacitinib [28]. Acceptable safety was also demonstrated and the a priori concern that JAK2 inhibition would result in high rates of anemia was not confirmed. A large Phase III program is currently underway. Decernotinib is a JAK inhibitor with high selectivity for JAK3. Phase II trials have confirmed efficacy [29]. Other JAK inhibitors are in earlier-phase trials.

Other small molecular agents in development for rheumatoid arthritis

The spleen tyrosine kinase (Syk) is another intracellular enzyme involved in cellular activation following binding to the B-cell receptor. Early-phase trials with the Syk-antagonist fostamatinib suggested efficacy [30] but later trials did not confirm this [31,32] and the development has been terminated. The selective inhibitor of phosphodiesterase-4 (PDE-4) apremilast was recently approved for the treatment of PsA. Although it has shown in vitro activity on RA synovial cells [33], no trials in RA have been published.

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Chapter 8

Strategies for the optimal use of biologic agents in rheumatoid arthritis

Introduction

When the first biologics for rheumatoid arthritis (RA) were developed it was clear that a large unmet medical need existed in this disease. A large segment of the patient population had failed all available conventional agents and had ongoing moderate or severe inflammation with progressive destruction of the joints. Even though some conventional approaches using more aggressive combinations of disease-modifying antirheumatic agents (DMARDs) seemed promising [1–3] it was in this context that the anti-tumor necrosis factor (TNF) biologics were first introduced, and predictably they were used primarily in patients with established and refractory disease. The effects were sometimes dramatic and often there was at least some level of success, and the enormous enthusiasm with which biologics were greeted in the field of rheumatology is readily explained by the results in these hitherto 'untreatable' patients.

But, because biologics also introduced major economic consequences for the healthcare systems in which they were used, rheumatologists and their societies were forced almost immediately to address the question for which patients the biologics should be used. The logical starting point was the patient who had failed numerous DMARDs and had highly active disease, but it was also recognized that patients who had failed two or more DMARDs were unlikely to respond to the next conventional agent. Meanwhile, the formal regulatory approval of anti-TNFs

R.F. van Vollenhoven, *Biologics for the Treatment of Rheumatoid Arthritis*,
DOI 10.1007/978-3-319-13108-5_8

was usually for patients who had failed methotrexate (MTX), and these two lines of reasoning converged so that biologics were mostly considered after a patient had failed to respond to MTX and at least one other DMARDs. This approach was subsequently codified in recommendations by the American College of Rheumatology (ACR) [4] and the European League Against Rheumatism (EULAR) [5]. One of the key questions for the practicing physician is therefore what treatment to choose for the patient who has failed MTX.

Treatment of the patient with an inadequate response to methotrexate

Several trials have addressed the question of which treatment should be chosen for patients with RA who have failed (or had an inadequate response) to MTX as the first-line treatment. The Swedish Swefot trial was carried out in patients with newly diagnosed RA who were all given MTX 20 mg/week for 3–4 months. If they did not achieve a Disease Activity Score (DAS)28 below 3.2 (low disease activity or remission) they were randomized to either the addition of two other conventional agents, sulfasalazine (SSZ) and hydroxychloroquine (HCQ), yielding the 'triple therapy', or the addition of anti-TNF in the form of infliximab (Figure 8.1).

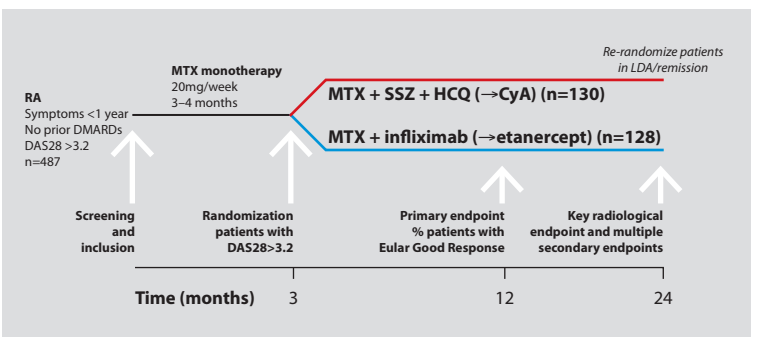

Figure 8.1 A randomized trial comparing an anti-tumor necrosis factor biologic with conventional combination therapy: the SWEFOT trial. The SWEFOT trial is a randomized trial investigating the addition of anti-TNF versus the addition of sulfasalazine and hydroxychloroquine for patients with an incomplete response to initial methotrexate. DAS28, Disease Activity Score 28; DMARDs, disease-modifying antirheumatic drugs; EULAR, European League Against Rheumatism; HCQ, hydroxychloroquine; MTX, methotrexate; RA, rheumatoid arthritis; SSZ, sulfasalazine. Van Vollenhoven et al [6].

The results showed that the addition of anti-TNF provided a somewhat greater clinical benefit after the first year of treatment (Figure 8.2) [6] and a radiologic benefit after 2 years [7].

It was also recognized that a substantial proportion of patients did respond to triple therapy, so that trying this option first might not be unreasonable. Moreover, the numerical benefit of anti-TNF therapy over triple therapy was rather small, and the clinical difference did not achieve statistical significance after 2 years of follow-up. Furthermore quality-of-life, functional, and employment outcomes in this trial did not differ between the arms [8,9]. The North American Racat trial addressed the same question as the Swefot trial but in patients who had an inadequate response to MTX after an average of 5 years of treatment, and assessed etanercept as the anti-TNF [10]. The primary outcome of this trial showed that triple therapy was as good as ('non-inferior to') anti-TNF therapy. The trial did show a difference between the two treatments with respect to several other outcomes, most notably the higher-end responses, the time to response, and a numerical radiologic difference. Perhaps most notably, the Racat trial also showed that patients who switched to triple therapy following failure on the anti-TNF still had as good a chance of responding to triple therapy as those who failed triple therapy and were then given anti-TNF.

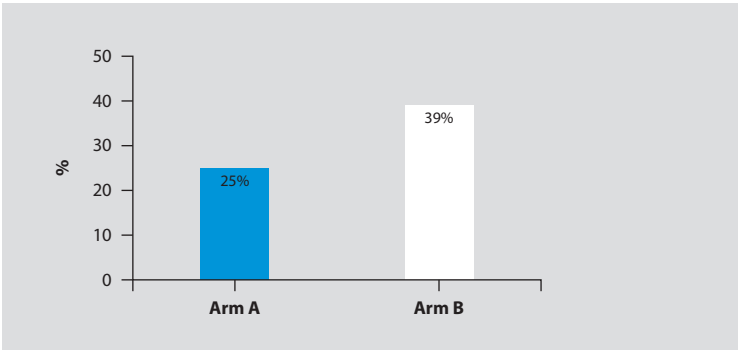

Figure 8.2 The primary outcome of the SWEFOT trial showing the proportion of patients achieving the EULAR Good Response after 1 year. EULAR, European League Against Rheumatism. Reproduced with permission from © Elsevier, 2009. All rights reserved. Van Vollenhoven et al [6].

Therefore, on pharmacoeconomic grounds, it may seem reasonable to require that patients are treated first with MTX and then triple therapy (or some other combination of conventional DMARDs) as a second line treatment before embarking on anti-TNF therapies (or other biologics). This approach has been formally recommended by some professional organizations [11] and it is also the requirement from many payer organizations. However, clinicians are often rather disinclined to use triple therapy and other conventional approaches, and it is perhaps fair to point out that the overall acceptance for biologics has been remarkably high and different from the often more frustrating experiences with conventional agents.

Treatment of the patients with newly diagnosed methotrexate-naive rheumatoid arthritis

Almost all of the approved biologics for RA have also been investigated in clinical trials where patients were given the biologic as the first antirheumatic treatment. In some trials the patients were defined by disease duration and by convention, trials where patients have a time from diagnosis less than two or three years are referred to as 'early RA trials'. In other trials, patients were selected based on the fact that they had not been treated with MTX, that they were 'MTX-naive', which in reality is mostly the same patient population. Either way, these trials invariably showed that the combination of the biologic plus MTX was superior to MTX alone in the cases of adalimumab [12,13], etanercept [14], infliximab [15], rituximab [16], abatacept [17], tocilizumab (Burmester et al, submitted) and also of tofacitinib [18]. Some of these trials also compared the biologic monotherapy with MTX, with more mixed results. Thus, adalimumab was clinically somewhat less efficacious than MTX but had better radiologic efficacy [12], etanercept was equivalent to MTX clinically and superior radiologically [14], while tocilizumab [19] and tofacitinib (Figure 8.3) [18] were both superior to MTX as monotherapy.

All these results notwithstanding, there are currently no professional societies, and certainly no payer organizations, that recommend biologics to be used as first-line therapy for RA. Why is this so? Clearly the cost of biologic therapy, being much higher than that of conventional

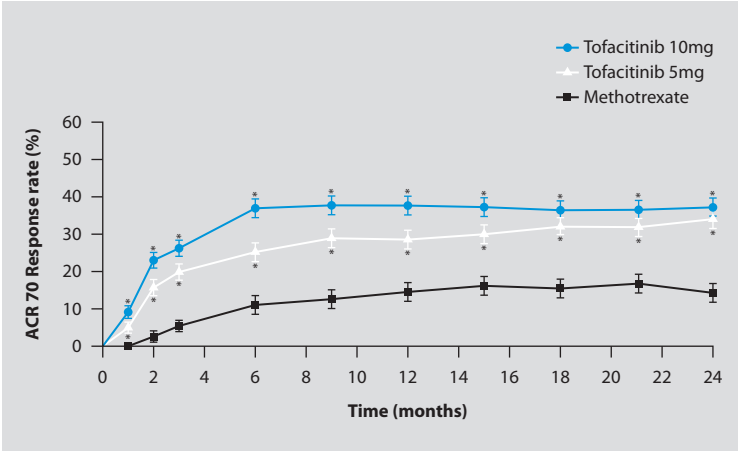

Figure 8.3 The ORAL-START trial compared tofacitinib with methotrexate in methotrexate-naive patients. ACR, American College of Rheumatology. Reproduced with permission from © Massachusetts Medical Society, New England Journal of Medicine, 2014. All rights reserved. Lee et al [18].

first-line therapy, plays a major role and it must also be recognized that a sizeable proportion of patients with RA has excellent responses to MTX (or other conventional DMARDs). For such patients the use of biologics would not be necessary and would entail greater risks of side-effects. The early introduction of biologics might also be perceived as 'dramatic' by the patient on account of their parenteral administration, although it would seem that the use of parenteral therapies in many other areas of medicine has made this route of administration more generally accepted over time.

Therefore, the early use of biologics is influenced almost exclusively by economic concerns, and it would be unfortunate if the treatments that are most optimal from a strictly medical point of view would be precluded simply on account of their cost. Fortunately, several developments are converging that may break this potential deadlock. For one thing, pricing developments of biologics are being favorably influenced by lower production costs, more competition, and the introduction of biosimilars. Perhaps more importantly, induction-maintenance therapies are increasingly being considered in the treatment of RA.

Induction-maintenance strategies in rheumatoid arthritis

The large Optima trial demonstrated that patients who are started on treatment with MTX plus adalimumab and who have a good response can often be continued on MTX alone and maintain the same good response (Figure 8.4) [13].

Similar results were more recently reported in the Preserve [20] and Prize [21] clinical trials with etanercept. The Avert trial also showed that a small proportion of patients could achieve a durable remission without any treatment following induction with MTX plus abatacept [22], a finding that is perhaps more scientifically important than clinically applicable. Based on these and other trials, it is possible to speculate that in the future it will be acceptable to initiate treatment with a biologic in combination with MTX for patients with newly diagnosed RA with the intention to discontinue the former once a stable low-disease activity status or remission has been achieved. Two key issues that still have to be resolved remain:

1. It is possible that the same results as seen in these induction-maintenance trials with biologics could be achieved through the early use of glucocorticoids (GCs), either in higher dosages

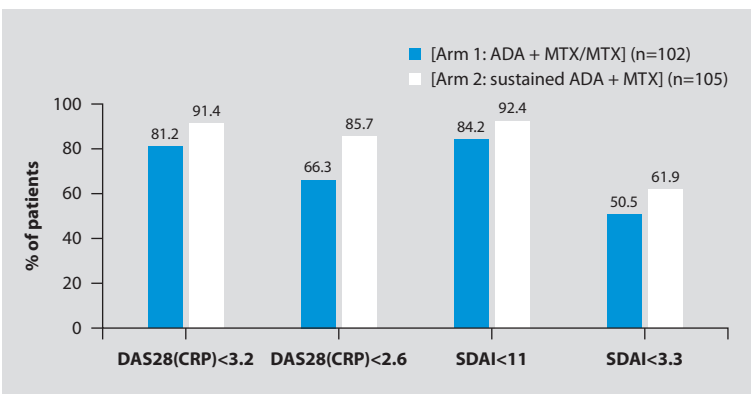

Figure 8.4 The OPTIMA trial. This trial compared, in patients with a good initial response to methotrexate + adalimumab, the continued treatment with both versus continuation with methotrexate alone. ADA, adalimumab; CRP, C-reactive protein; DAS28, Disease Activity Score 28; MTX, methotrexate; SDAI, Simplified Disease Activity Index. Data taken from [13].

with a subsequent taper [23], or in the form of multiple intra-articular injections [24]. This possibility is being investigated formally in several trials, including in the ongoing NORD-STAR clinical trial [25].

2. There has to be a good plan for those patients who are started on MTX plus biologic and who have a clear clinical response but who do not achieve a satisfactory disease state. For such patients the treatment obviously cannot be de-escalated but it would also be incorrect indefinitely to continue a treatment that is only partially effective. For these patients a suitable therapeutic algorithm must be developed.

Switching after failing an anti-tumor necrosis factor

All the justifiable excitement about biologics notwithstanding, a sizeable proportion of patients with RA do not have a sufficient response to the first biologic that they are treated with. For such patients, a switch to another biologic is generally recommended (although it should be recognized that switching back to conventional DMARDs may not be unreasonable, as recently shown in the Racat trial [10]).

In current practice the first biologic is often an anti-TNF. It could be argued that this need not be so (most biologics are approved as a first biologic), indeed abatacept, rituximab, and tocilizumab are cited as appropriate choices for a first biologic according to the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommendations and there is some use of these as first biologics in clinical practice. However, the years of practical experience with the first three anti-TNFs make them a logical choice for many practitioners. Therefore, the most clinically relevant question is what to do when the first anti-TNF fails.

In this case, the use of a second anti-TNF is supported by mixed levels of data. Only golimumab was formally tested in a randomized trial for patients who had failed a prior anti-TNF, with a clear positive result. The primary outcome of this trial, ACR20 at week 14, was achieved by 35% of patients on 50 mg golimumab and 38% patients on 100 mg golimumab versus 18% patients on placebo, with odds ratios of 2.5 [95% CI 1.5–4.2] and 2.8 [1.6–4.7], respectively [26]. For adalimumab, Bombardieri et al [27] showed that in

patients who had previously been treated with etanercept or infliximab, 60% achieved an ACR20 after 12 weeks and 33% an ACR50 response; 76% achieved a moderate and 23% a good EULAR response. In addition, 12% achieved a DAS28 <2.6, indicating clinical remission, and 13% achieved a HAQ DI score <0.5. For certolizumab-pegol, Weinblatt et al [28] showed that the primary endpoint, ACR12 at week 12, was achieved by 51.1% on active treatment vs 25.9% on placebo (P<0.001); there were also significant differences in HAQ-DI, DAS28 change from baseline, and ACR50. Thus for adalimumab [27] and certolizumab-pegol [28] evidence was derived from sub-group analyses in larger trials while the evidence for the original two anti-TNF agents, etanercept and infliximab, comes from observational studies only. Nevertheless, the totality of the evidence suggests that choosing a second anti-TNF is not unreasonable.

For the patient who has failed a first anti-TNF it is also reasonable to switch to a biologic with a different mechanism of action, and evidence from randomized trials is available to support this for abatacept [29], rituximab [30], tocilizumab [31], and for tofacitinib as well [32]. In all these instances, it should be recognized that the trials established the superiority of the biologic versus placebo in patients who had previously failed an anti-TNF. The trials did not demonstrate that the new treatment was superior to what would have happened in terms of patient response if the patient had 'stayed the course' with the previous biologic.

It has been hoped that the exact pattern of failure to the first anti-TNF could provide guidance towards the choice of the second biologic [33], but this has been hard to implement into practice. Similarly, some have argued that therapeutic drug monitoring, or even the detection of anti-drug antibodies, could provide guidance in the clinical situation [34] – but this has not been integrated widely into clinical practice either. At this time, the choices discussed here remain largely empirical. A model for suggested switching between biologics is shown in Figure 8.5.

Dose optimization with biologics: dosing up, dosing down

While some biologics are approved as a single 'one-size-fits-all' dosage, for others a range of doses is available, most notably for infliximab

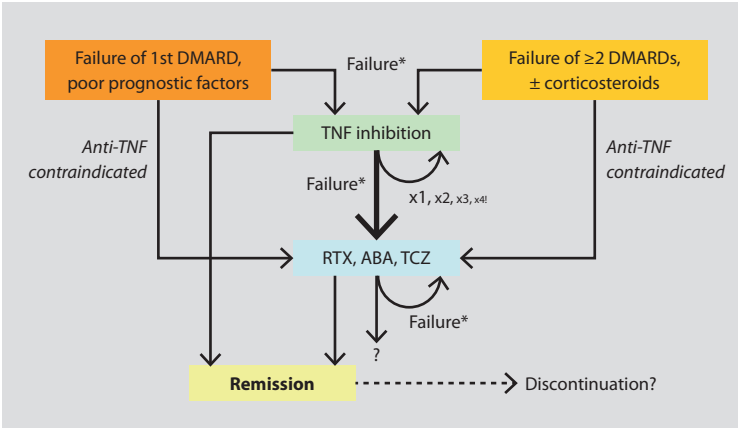

Figure 8.5 Switching between biologics. This simple schema suggests how patients can be treated consecutively with different biologics. There are only limited data to guide such therapy choices and the decisions remain largely empirical. ABA, abatacept; DMARD, disease-modifying antirheumatic drugs; RTX, rituximab; TCZ, tocilizumab; TNF, tumor necrosis factor. Reproduced with permission from © John Wiley and Sons, 2011. All rights reserved. Chatzidionysiou and van Vollenhoven [35].

(3 to 10 mg/kg), adalimumab (40 mg weekly or biweekly), and golimumab (50 or 100 mg monthly). This is often interpreted as an option for patients who on the lower dose do not achieve a satisfactory response, whereby a dose or frequency increase can result in a better clinical outcome. However, this may not be the case. For infliximab, a randomized trial failed to demonstrate a benefit for a dose increase from 3 to 6 mg/kg [36] and in the Premier trial the weekly dose was not superior to the biweekly dose [12]. For the clinician it may be hard to resist the temptation for dosing-up (if the drug reimbursement system allows it) but there may be additional safety issues with the higher dosages [37]. Thus, a dose increase should be performed only under compelling circumstances and with a strict intention to monitor the results closely.

Dosing-down, on the other hand, has become a topic of considerable interest as several recent trials have suggested that this may indeed be a possibility for several biologics. Some of these trials have focused on patients with newly diagnosed RA and have been discussed above under the heading of induction-maintenance. But even in patients with established RA some recent trials have evaluated the possibility of

dosing-down in patients with a stable disease state of low activity or remission. Thus, in the Dosera trial, patients on etanercept who were continued on 25 mg weekly fared only marginally worse than those who continued with 50 mg weekly. In the DRESS [38] and STRASS (Fautrel, submitted) trials a large majority of patients were able to increase the dosing intervals for etanercept and adalimumab while maintaining a low disease activity state, and in a separate study it was suggested that the same could be true for patients on tocilizumab [39].

Head-to-head comparative studies of biologic agents

Only a small number of true 'head-to-head' trials have been performed with biologics, but they have demonstrated interesting results. In one trial, intravenous abatacept achieved similar ACR responses as infliximab after 26 weeks, albeit with a slight delay, but numerically higher responses after 52 weeks [40]. In this trial, the numbers of several adverse events, including infections, were lower for abatacept. In another head-to-head trial,abatacept was compared to adalimumab, both given subcutaneously and both on a MTX background [41]. In this trial the responses were virtually identical over the entire first year of the study, and the adverse events were also similar. Likewise, the small-molecular biologic-like agent tofacitinib achieved at least similar efficacy as adalimumab in a trial with patients who were also on MTX [42]. Finally, in a Phase IV randomized study, tocilizumab was shown to be superior to adalimumab when both were given subcutaneously as monotherapy [43].

Determining which therapy is most appropriate for an individual patient: personalized therapy

With seven or eight conventional DMARDs, nine approved biologics and, in some countries, a small-molecular biologic-like drug available in clinical practice, the choices are becoming overwhelming: how should we choose the right treatment for each patient? Rheumatology has remained an empirical clinical specialty where much of what is done in daily practice has the character of 'trial-and-error'. It would be attractive to be able to choose more rationally and select a treatment for the individual patient

that has a high a priori likelihood of providing optimal results. It is doubtful that clinical trials, no matter their importance, will be able to contribute much in this regard: their results represent findings at the group level and do not indicate for which individual patient the result is most likely to be applicable. However, some inroads are being made into the coveted field of personalized medicine even in rheumatology. Among the more encouraging developments, the following stand out:

The use of biomarker panels for characterizing patients at the molecular level has gone from being mostly a laboratory exercise to being clinically applicable. A first biomarker panel is now approved by the US FDA for measuring disease activity in RA. This panel, named VectraDA, was shown in a recent study to provide better individualized prediction of the risk for radiographic damage in early RA than C-reactive protein

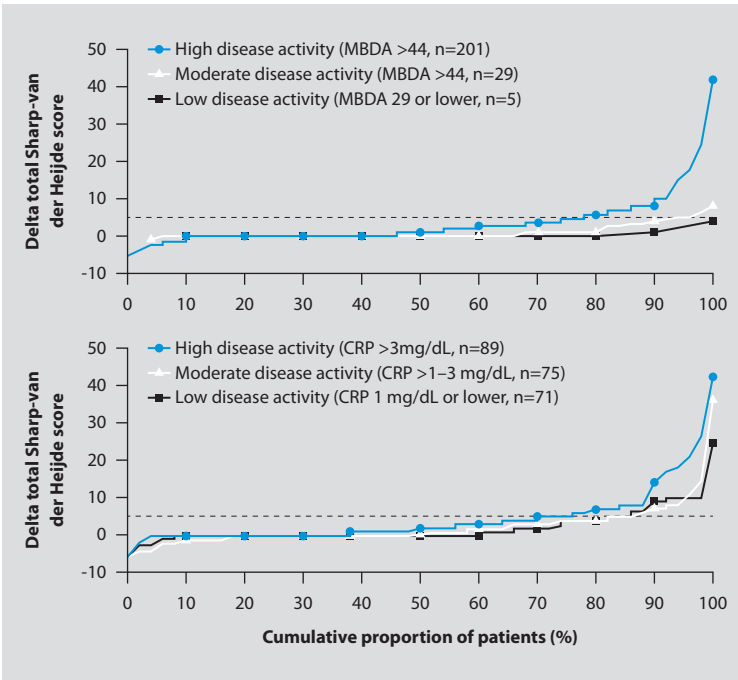

Figure 8.6 The Multi-Biomarker Disease Activity (MBDA; Vectra DA) score (left panel) predicted the risk of radiographic progression more accurately than the C-reactive protein (CRP; right panel), the erythrocyte sedimentation rate or the Disease Activity Score 28 (not shown). Reproduced with permission from © BMJ Publishing Group Ltd, 2014. All rights reserved. Hambardzumyan et al [44].

(CRP), erythrocyte sedimentation rate (ESR), or DAS28 (Figure 8.6) [44]. Several other biomarker panels are in late-stage clinical development.

The use of more advanced imaging is allowing more accurate characterization of the individual patient's inflammatory state. Refinements of ultrasound technology have made it a useful tool in daily practice and it was recently proven to increase diagnostic accuracy in early arthritis [45]. Other innovations, including fluorescent optical imaging [46], may also allow better individualized therapy decisions.

There is a growing interest in harnessing the healthcare environment itself for providing the data that will help achieve more individualized medicine [47,48]. By tapping into the vast resources of the 'learning healthcare environment', the large number of nearly-random decisions made by physicians every day can be sources of information that will ultimately lead to better care and better outcomes for each individual patient.

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Chapter 9

Considerations for special patient populations

Special considerations in the pregnant patient

General pregnancy considerations

Patients with rheumatoid arthritis (RA) often experience marked spontaneous improvement during pregnancy. This classical clinical observation, documented already by Philip Hench in the 1930s [1], has been confirmed in several studies [2,3]. Fortunately therefore the difficulties of treating RA are sometimes – but not always – alleviated at a time when safety considerations must take into account not only the patient but also her child. Nevertheless, most patients with RA do need some form of treatment during pregnancy [3]. Moreover, patients with RA who are considering pregnancy do rightfully wish to plan ahead and be informed of the potential consequences of antirheumatic treatments in the case that a pregnancy might ensue. It was shown that although a majority of rheumatologists indicate that they discuss family planning and pregnancy with their patients, many patients feel that they have not been provided with sufficient information in this regard [4] – perhaps a reflection of the complexity of the issues rather than of the time spent on discussing them. Importantly, medications with long half-lives such as leflunomide and some biologics, or those that persist in tissues, such as methotrexate (MTX), pose the concern that even if the treatment is stopped when a pregnancy has occurred, exposure to the drug during the early phase of pregnancy has already taken place and this exposure may continue for several more weeks or even months. For conventional

R.F. van Vollenhoven, *Biologics for the Treatment of Rheumatoid Arthritis*,
DOI 10.1007/978-3-319-13108-5_9

disease-modifying antirheumatic drugs (DMARDs), these considerations have resulted in the general recommendation that MTX should be stopped 3–6 months before conception is attempted, that leflunomide must be 'washed out' with cholestyramine in advance, but that other DMARDs can be continued up until the time of conception or even during pregnancy (reviewed in [5]).

As far as biologics are concerned, it must be emphasized in the first place that none of them are approved by regulators for use during pregnancy. This mostly reflects the fact that established pregnancy and planned pregnancy are universally applied as exclusion criteria in clinical trials, and that it takes a long time and painstaking analyses of additional information from observational and registry data to arrive at solid conclusions. Psychologic and societal factors surrounding the topic of family planning and pregnancy also play a role in dictating strongly risk-aversive policies. Nevertheless, it can also be pointed out that there are no known risks during pregnancy with any of the biologics. For the anti-tumor necrosis factor (TNF) therapies and anakinra the official US Food and Drug Administration (FDA) category B is applied, which means that there are no indications of risk in animals but that adequate and well-controlled studies in pregnant women are lacking. The other biologics belong to category C, indicating that animal studies have shown adverse effects on fetuses and that adequate and well-controlled studies in pregnant women are lacking.

Safety data on biologics and pregnancy from animal models

Only few studies in animal models have been done with properly equivalent monoclonal antibodies or other biologics, but in these no adverse effects on fetal development were noted [6,7].

Fetal exposure to biologics: transplacental diffusion and transport

During the first trimester, only small amounts of immunoglobulins and other large proteins reach the embryonal circulation through passive diffusion [8]. During the second and third trimesters active transport of immunoglobulins across the placenta takes place, where the Fc portion of the immunoglobulin is bound to the neonatal Fc receptor FcRn. Indeed,

infliximab was present in the fetal circulation of a woman with Crohn's disease who was treated with infliximab during pregnancy [9]. Among the anti-TNF agents, certolizumab lacks an Fc portion and is not expected to be transported across the placenta. In vitro studies demonstrated that transport was highest for the monoclonal antibodies infliximab and adalimumab, somewhat lower for etanercept, and lowest for certolizumab. A study of cord blood from newborn children whose mothers had been exposed to biologics also showed that the concentrations of adalimumab and infliximab were higher in the cord blood than in the maternal circulation, whereas for certolizumab the reverse was found [10,11].

Observational data on anti-tumor necrosis factor exposure during pregnancy

Observational studies of biologic exposure during pregnancy have so far been mostly reassuring. During the first years following the introduction of infliximab, 146 cases of exposure before or during pregnancy were documented, with pregnancy outcomes available in 106 women. Most had Crohn's disease and only eight had RA. No differences from expected rates were noted for numbers of live births, miscarriages and terminations [12]. Among 23 patients with RA who were followed in the British registry and who were exposed to etanercept (17), infliximab (3) or adalimumab (3), four had first-trimester miscarriages and the others had live births without birth defects [13]. In 2009, the FDA reported on cases of spontaneously reported adverse events in women exposed to anti-TNF agents before or during pregnancy. Around 60 congenital abnormalities had been reported, but having no denominator for exposure it was impossible to know if this rate was increased; however, it was noted that 19 of the reports concerned the VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal, renal, and limb abnormalities), which was considered a 'signal' inasmuch as this particular group was overrepresented in the total sample [14]. However, in a later study on 83 women exposed to anti-TNF during pregnancy there was no difference in the rate of major congenital abnormalities versus disease-matched controls and there were no cases of VACTERL [15]. In the TREAT registry 142 women with Crohn's disease were exposed to infliximab; there was no difference

in the rate of live births or of congenital abnormalities [16]. Recently, pregnancy results in a large cohort of adalimumab-exposed women were presented. This included 32 women who had used the treatment throughout pregnancy. The rates of major congenital defects, preterm delivery, and fetal growth retardation were comparable to RA controls, and there were no differences in minor malformations either [17]. A small number of cases of (pre-) pregnancy exposure with certolizumab were described without apparent adverse consequences [18].

Two systematic literature reviews on anti-TNF exposure during pregnancy concluded that there were no associations with congenital abnormalities or other untoward fetal outcomes [19,20]. These reassuring data should be interpreted with caution, inasmuch as the vast majority were derived from women who stopped anti-TNF treatment when pregnancy was documented.

A single case report underscores another type of risk posed by the use of biologics during pregnancy: an infant born to a mother with Crohn's disease who was treated with infliximab during pregnancy was given the Bacillus Calmette-Guérin (BCG) vaccination (as was routine in that country). Sadly, the vaccination led to a systemic infection with the attenuated bacilli and the infant died [21]. It was realized too late that infliximab, with a serum half-life of 10 days and probably much longer in the infant, was still present in the circulation when the vaccine was administered and it interfered with the normal mechanisms for containing the mycobacteria.

Exposure to non-anti-tumor necrosis factor biologics during pregnancy

Three cases have been reported of women who used anakinra throughout pregnancy for adult-onset Still's disease; one birth was complicated by placental retardation but there were no fetal abnormalities [22,23]. Rituximab during pregnancy has been studied comparatively well, although mostly in the setting of lymphoma. It crosses the placenta and has in case reports been associated with lymphopenia and B-cell depletion in the neonate [24–26]. Among 231 pregnancies in exposed women there were 22 premature deliveries, two infants had major congenital abnormalities, 11 had hematologic abnormalities and four suffered

from infections [26]. Most of these patients had been treated with other cytotoxic or immunosuppressive medications as well. A small number of exposed infants were studied and found to have normal immunoglobulin G (IgG) responses to vaccines. A single abstract described 32 patients with (pre-) pregnancy exposure to tocilizumab [27], mostly in combination with MTX. Seven spontaneous abortions occurred and one child died after birth from complications ensuing from placenta praevia.

Infant exposure to biologics during lactation

Maternal immunoglobulins are actively excreted into the breast milk and one might expect this to apply to the monoclonal biologics. However, apart from the first days of life, proteins from breast milk are digested in the stomach and there is therefore little a priori concern about neonatal exposure to the intact protein after those first days. In one patient etanercept was demonstrated in the breast milk but not in the breast-fed infant [28]. By contrast, in several infliximab-treated women the drug was not detected in breast milk or in the infant [9,29] and adalimumab levels in the breast milk were low in another case [30]. These observations are particularly important given the fact that many patients with RA experience significant postpartum flares of their disease [3,31,32], which may make it necessary to resume previously effective therapies rather soon after delivery.

Exposure of men to biologics prior to or at the time of conception

In men treated with various anti-TNF agents for ankylosing spondylitis, sperm abnormalities were not more common than in healthy controls [33]. In the TREAT registry, infliximab treatment of men was not associated with congenital abnormalities [16]. Two smaller series had similarly reassuring results [12,34].

Special considerations in the pediatric patient

Juvenile inflammatory arthritis

The treatment of inflammatory joint diseases in infants, children, and adolescents has benefited tremendously from the introduction of biologics into practice. Despite the added concerns that long-term treatment

entails in these patients, and worries about potential effects on growth and development, experiences in practice have been overwhelmingly positive and biologics have become widely accepted treatments in pediatric rheumatology practice.

Juvenile inflammatory arthritis (JIA) is a heterogeneous group of diseases [35]. The least common form is the systemic onset form of JIA, which can have its onset during the first years of life and is typically characterized by high spiking fevers, rash, lymphadenopathy, and hepatosplenomegaly. The most common form of JIA is the pauci-articular or oligo-articular JIA type which is typically seen mostly in younger girls who are usually rheumatoid factor (RF)-negative but may be anti-nuclear antibody (ANA)-positive. In addition to inflammation in the joints about half the children also have uveitis. The polyarticular form of JIA may be RF-positive or -negative and, especially the former, may be considered the equivalent of RA with onset during the childhood years. Both the systemic and the pauci-articular form of JIA can secondarily progress to the polyarticular form, heralding a worse prognosis. Here, the role of biologics in the treatment of polyarticular JIA will be discussed in detail, this form being most similar to RA in adults. For more information on the treatment of systemic and pauci-articular JIA the reader is referred to several excellent reviews [36–38].

Traditionally, the treatment of JIA relied heavily on non-steroidal anti-inflammatory drugs (NSAIDs), and to a lesser extent on glucocorticoids (GCs) and DMARDs. Importantly, whereas these three treatment categories were found to be applicable to all types of JIA (but with limited success) the biologics seem to be more distinctly efficacious for one type of JIA or another. Thus, while most patients with polyarticular JIA can be treated effectively with anti-TNF biologics, for the systemic form the antagonists of interleukin (IL)-1 and IL-6 seem to be superior.

Clinical trials in juvenile idiopathic arthritis: randomized withdrawal trials

Traditional placebo-controlled studies are considered ethically less appropriate for children and adolescents than they are for adults. Instead, academic investigators and regulators have supported the withdrawal

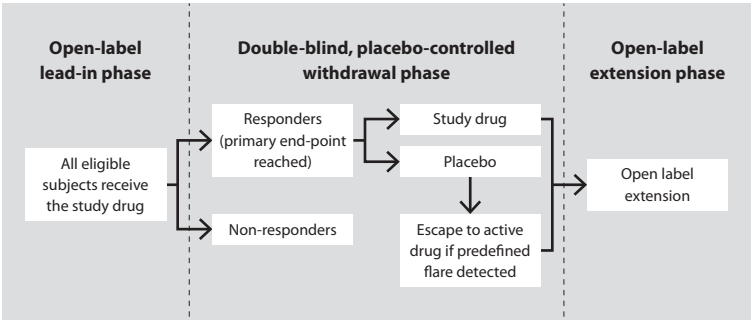

Figure 9.1 The randomized withdrawal design has been used frequently in trials of new medications for pediatric patients. At the end of the open-label treatment period, those patients who have responded are randomized to continue active treatment versus placebo. The rate of subsequent relapses or flares is the primary outcome. Retreatment with the active compound in case of a relapse is usually also included in the protocol.

trial design (Figure 9.1) where all included patients are initially started on the study medication, and those who respond are then randomized to continue with drug versus placebo. The rate of relapse (flare) after randomization is the primary outcome. This design offers many attractive features: all participating patients are started on the treatment (for which there must be good reasons to assume a benefit); only those who respond initially are continued so that exposure to an ineffective drug is limited; the randomized withdrawal provides solid evidence for efficacy albeit in a slightly indirect manner; and the trial can feature a re-treatment phase for those who flare after discontinuation; knowing whether this is successful is an important piece of information for any treatment.

Anti-tumor necrosis factor biologics in polyarticular juvenile idiopathic arthritis

The first three approved anti-TNF agents have been tested in patients with polyarticular JIA and an inadequate response to MTX. A randomized withdrawal trial of etanercept yielded an initial response of 74% with flares on continued treatment seen in 28% versus 81% for placebo [39]. In a similarly designed trial, 74% of patients initiated on adalimumab monotherapy and 94% of those started on adalimumab plus MTX achieved an initial response, and of these significantly more maintained the response on active drug than on placebo [40]. Both adalimumab and

etanercept have been approved for use in this patient population. A similarly designed clinical trial of infliximab did not achieve significance in the primary endpoint [41] and infusion reactions and immunological side effects were frequent. Thus, infliximab has not been approved for JIA, but many experts believe it is similarly efficacious to the other anti-TNF agents and continue using it 'off-label'. This view was also supported by a more recent randomized study [42]. The newer anti-TNFs have not been formally tested in JIA.

Side effects with the anti-TNF therapies in polyarticular JIA have been limited and mostly mild. Longer-term follow-up has likewise been mostly reassuring [43]. However, a report by the FDA leading to a 'black-box' warning suggested a relatively high prevalence of lymphoma in children and adolescents treated with anti-TNF agents [44] including the rare hepatosplenic T-cell lymphoma (HSTCL). A subsequent study from Sweden demonstrated that the risk of lymphoma is generally elevated in JIA irrespective of treatment [45], and it was also noted that the 10 patients who developed HSTCL had also received other immunosuppressive therapy known to be associated with this rare disease [46]. Moreover, a large study based on claims data from the US showed that JIA itself is associated with an elevated risk for malignancies that does not seem to be increased further by anti-TNF therapies [47].

Other biologics in polyarticular juvenile idiopathic arthritis

Anakinra was not effective in one trial in polyarticular JIA [48]. By contrast, abatacept was efficacious in a randomized trial in polyarticular JIA [49] and is approved for this indication. It seems to be similar to anti-TNF agents in efficacy and has a favorable side-effect profile. Tocilizumab was also effective in a randomized trial in polyarticular JIA [50]. It was associated with a higher number of safety issues and adverse events, and the benefit/risk remains less clear in this population. Rituximab has not been tested for JIA in randomized trials. A large case series suggested efficacy but concerns over long-term B cell depletion and hypogammaglobulinemia have tempered enthusiasm for use in children [51,52].

Biologics in pauci-articular and in systemic juvenile idiopathic arthritis

Although pauci-articular JIA is the most prevalent form of JIA there are relatively few studies specifically examining biologics in this patient population. The results in these patients appear to be broadly similar to those in polyarticular JIA, but there is a difference with respect to the important aspect of uveitis. It appears that while adalimumab and infliximab are effective in treating uveitis [53–55], treatment with etanercept may paradoxically increase the risk of this complication [43,56,57].

The IL-1 antagonist anakinra is effective in various febrile syndromes occurring in young children. In systemic onset JIA (sJIA), anakinra was shown in several trials to be effective [58–60]. The anti-IL1 monoclonal canakinumab also showed very good efficacy in sJIA [61,62]. Both anakinra and canakinumab are approved for this indication. Perhaps unexpectedly the IL-1 antagonist rilonacept was not more effective than placebo in a small randomized trial and was associated with numerous side effects [63]; it is not approved for use in children. Finally, an important role for IL-6 in the immunopathogenesis of sJIA is supported by the demonstration that tocilizumab was superior to placebo in a randomized withdrawal trial; it is approved for this indication [64].

Special considerations in the elderly patient

Patients at the higher age ranges present particular challenges to the practicing physician. There are often multiple comorbidities and multiple concomitant treatments. Metabolism is altered in older people but it is often hard to obtain quantitative guidance on dosing based on age. Although RA is not necessarily more severe in elderly patients, the disease, having been sometimes present for decades, does result in more extensive joint damage, which is often confounded by osteoarthritis. Both osteopenia and weakness of the muscles and other soft-tissue structures (sarcopenia) add to the overall effect on physical function and to the risk for complications. Fortunately, it appears that biologics are as effective in elderly patients with RA as they are in the overall population of patients [65]. Thus, in both subanalyses from clinical trials and observational studies it appears that the elderly respond equally well, and do

not have more side effects, to treatment with adalimumab, etanercept, infliximab, rituximab, or tocilizumab [66–76]. Although not formally studied, it stands to reason that strategies aiming at dose reduction may also be considered in the elderly patient.

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Chapter 10

Conclusions and future outlook

Historical perspective

Forty years ago this year George Kohler and Cesar Milstein published an article in *Nature* describing a method for "continuous cultures of fused cells secreting antibody of predefined specificity" Figure 10.1 [1].

Behind this innocuous title lay a methodological discovery of momentous importance for the entire field of medical research and therapeutics. It became possible to produce unlimited quantities of monoclonal antibodies

Figure 10.1 Cesar Milstein and George Kohler discovered a method for generating monoclonal antibodies. Their discovery gave them the Nobel Prize, and made possible the development of therapeutic monoclonal antibodies. Reproduced with permission from © Medical Research Council Laboratory of Molecular Biology, 2015. All rights reserved. Medical Research Council Laboratory of Molecular Biology .

R.F. van Vollenhoven, *Biologics for the Treatment of Rheumatoid Arthritis*,
DOI 10.1007/978-3-319-13108-5_10

that would specifically target whichever molecule or cell- type was desired. It was realized early on how this could translate into both major basic scientific advances and important new therapy approaches. During the first decade the focus was mostly on methodological refinements and the increasing use of monoclonal antibodies as indispensable research tools. However, the promise of using monoclonal antibodies as therapeutics was 'in the air', and the first experiences of treating lymphoma with anti-idiotypic monoclonals were published in 1982 [2]. In 1985 the anti-CD3 antibody muromonab became the first approved therapeutic monoclonal and was used for many years to treat acute transplant rejection [3,4]. Its main drawback lies in the sometimes severe allergic reactions that ensue from the administration of a xenogeneic molecule. Therefore, around the same time a technology was developed for creating chimeric monoclonal antibodies, whereby the murine antigen-binding site was grafted onto a human immunoglobulin (Ig)-frame, a technology that led to a large number of therapeutic monoclonal antibodies (designated by the –ximab ending). Indeed, the first published report on the treatment of rheumatoid arthritis (RA) with a monoclonal antibody featured a chimeric monoclonal targeting the CD4 molecule on T-helper (Th) cells [5]. After initial enthusiasm this approach fell by the wayside, but the first report of using anti-tumor necrosis factor (TNF) arrived not much later [6]. Around the same time, other approaches toward developing biologic molecules for therapeutic uses were emerging. The naturally occurring interleukin (IL)-1 receptor antagonist had been cloned and was developed as a therapeutic [7]. Technology for further refinement of monoclonals through 'humanization' (-zumab) was developed, as well as phage display approaches that yielded fully human monoclonal antibodies (-mumab). Some further innovations are currently in early stage human trials, such as the use of bi-specific monoclonal antibodies [8], or the use of 'modular' molecules with an immunoglobulin-like structure but where each domain is created separately [9].

Future perspective

Many ongoing developments will certainly lead to additional treatment options for RA, some of which could be considered extensions of the current treatment paradigms: for example, additional refinements in cytokine

antagonism and the targeting of other cell-surface molecules. However, completely different approaches are also being considered and some will hopefully result in additional advances in therapeutics; among these could be the activation of naturally occurring regulatory T cells (Tregs), neuro-immunomodulatory approaches, cell-based therapies, and others. Importantly, realistic future developments in the therapy for RA need not only target the inflammatory process. I expect important practical applications in the field of regenerative medicine, which is currently seeing rapid advances [10–12]. Such approaches could help those patients in whom RA has already caused structural damage, either because the damage occurred before they were adequately treated or when this happened despite our best efforts.

Additional cytokine targets

While the number of anti-cytokine biologics that are in clinical use today is substantial there are obviously many more cytokines that could be targeted. Indeed, selective inhibitors of the IL-17 pathway are in late-stage development for the treatment of psoriasis [13–16], RA [17], psoriatic arthritis [18,19], and spondyloarthropathies [20] and the first of these, secukinumab has been approved for treating psoriasis both in Europe and in the US. Similarly, the monoclonal antibody mavrilimumab, which targets the granulocyte-monocyte colony stimulating factor, which has important immunoregulatory functions, showed efficacy in a trial in RA [21].

In addition, there is a large number of novel anti-cytokine approaches currently under investigation at the preclinical stage or in early-phase human trials. Unfortunately, it has become clear that our ability to predict therapeutic benefits on the basis of in vitro or animal experimental data has remained rather limited, and it remains to be seen which approaches will make it to the clinic even as many others will fall by the way-side.

Activation of regulatory T cells

An entirely different conceptual approach to autoimmunity would be the activation of Tregs. Extensive animal experience suggests the feasibility of this approach but human trials have run into difficulties. The activating anti-CD28 monoclonal antibody TGN1412 caused severe side effects in its first-in-human trial, clearly caused by the widespread activation of inflammatory

pathways [22]. This delayed further developments in this direction by many years. However, more recently the monoclonal antibody tregalizumab, which is directed against a specific epitope on the CD4 molecule, was shown to activate Tregs only (Figure 10.2) [23] and was safe in Phase I trials in healthy volunteers. A small trial in RA [24] suggested possible efficacy but a larger trial in RA [25] was recently reported to have failed. Nonetheless, if an approach targeting Tregs were to be successful in one disease, it would suggest additional applications in many other autoimmune diseases as well.

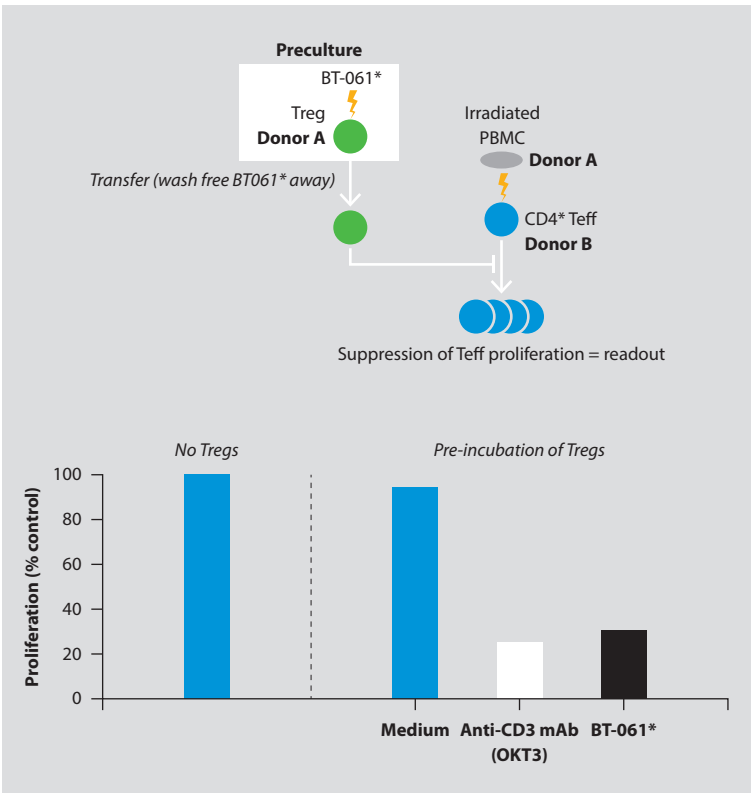

Figure 10.2 The monoclonal tregalizumab, here designated BT-061, specifically activates regulatory T-cells (Tregs) as was shown in various in vitro assays. In this experiment, the addition of Tregs that were pre-incubated with tregalizumab suppressed the mixed lymphocyte reaction nearly as effectively as Tregs pre-incubated with broadly stimulatory anti-CD3 antibodies. Tregs, regulatory T cells. Reproduced with permission from © Biotest AG, Dreiech, Germany, 2015. All rights reserved. Biotest AG [26].

Neuroimmunomodulatory approaches

The discovery of the 'inflammatory reflex' [27] may open up a completely new way of treating autoimmunity. In mice immune responses in the spleen are 'monitored' by the central nervous system through afferent vagal pathways and, perhaps even more importantly, regulated through efferent vagal pathways acting through macrophages on T cells (Figure 10.3) [28–30].

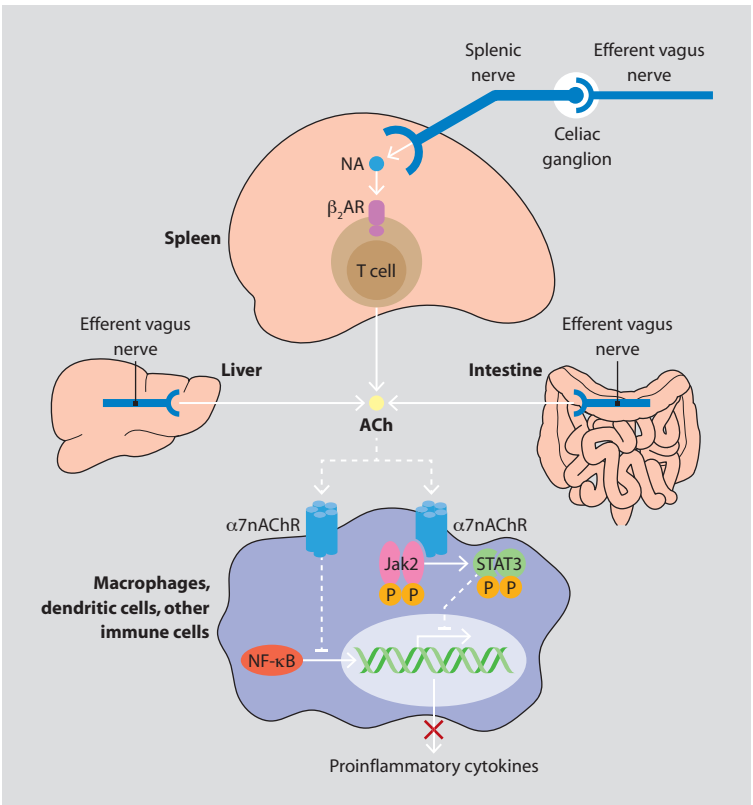

Figure 10.3 Molecular mechanisms of cholinergic control of inflammation. Efferent vagus nerve activity is translated into catecholamine-mediated activation of T-cell-derived acetylcholine release in the spleen and into direct acetylcholine release from efferent vagus nerve endings in other organs. Inhibition of NF-κB nuclear translocation and activation of a JAK2-STAT3-mediated signalling cascade in macrophages and other immune cells are implicated in cholinergic α7nAChR-mediated control of proinflammatory cytokine production. ACh, acetylcholine; β2AR, β2 adrenergic receptor; JAK2, Janus kinase 2; α7nAChR, α 7 nicotinic acetylcholine receptor; NA, noradrenaline; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3. Reproduced with permission from © Nature Publishing Group, 2012. All rights reserved. Pavlov and Tracey [30].

It has been suggested that similar mechanisms might occur in humans and a small pilot study [31] was recently initiated in which subjects with RA received an implantable device in the chest/neck region that electrically stimulates the vagal nerve in the hopes of down-regulating systemic inflammation in this manner. In this very small group of patients some improvements were noted, but complications with the procedure did occur and it would seem that considerable hurdles, both practical and scientific, will need to be overcome before this approach could reach clinical application.

Cell-based therapies

There is an increasing field of treatment approaches based on the infusion of modified autologous or allogeneic cells. The advantages of cell-based therapies could, in theory, be significant but tremendous technical and practical issues must also be overcome. Perhaps the most interesting approach that is currently in early-phase trials is the use of mesenchymal stromal cells [32]. These cells, which can be engineered to develop into cells belonging to various tissue types, exhibit anti-inflammatory and immunosuppressive properties that make them attractive for the treatment of systemic inflammatory diseases by virtue of the combined benefits of this general regulatory effect and the tissue or organ tropism that would be conferred by their particular cellular differentiation in relationship to the disease under study.

Biosimilars

As already discussed earlier in this book, several of the biologics that are in use for RA are losing patent protection and many companies are developing similar molecules. The first two biosimilars for infliximab (being the same substance but marketed by two companies under different names) have now been approved in Europe. Although some questions continue to be asked about the interchangeability of these biologic products the economic pressures to lower costs are such that there is little doubt that biosimilars will play an increasing role in the treatment of inflammatory diseases such as RA.

Future prospects for treatment strategies in rheumatoid arthritis: 'treating to target'

In addition to ongoing efforts to identify better therapeutics for RA, the re-evaluation and reassessment of treatment strategies for RA will continue and may lead to entirely new treatment paradigms. The principle of treating to target was originally derived from diseases such as hypertension, where trials demonstrated that long-term outcomes were better if clinicians clearly identified the blood pressure that they wanted to achieve and took action to achieve it. For RA, at least two randomized trials also provided direct evidence that such an approach, based on targeting a certain level of the Disease Activity Score (DAS), yielded better long-term results (Figure 10.4) [33,34].

Formal Treat-to-Target (T2T) guidance for RA was published several years ago and the principle has increasingly been implemented [35]. Similar recommendations have also been developed for several other rheumatic diseases [36,37]. It should be emphasized that T2T is not only about choosing a target, but also about deciding on how and when to measure that target, and about the principle that failure to achieve the target should lead to a therapeutic change in most cases.

Epilogue

In summary, the progress of biologic therapies for RA has been nothing but remarkable. Will this trend continue? On the one hand, our insights

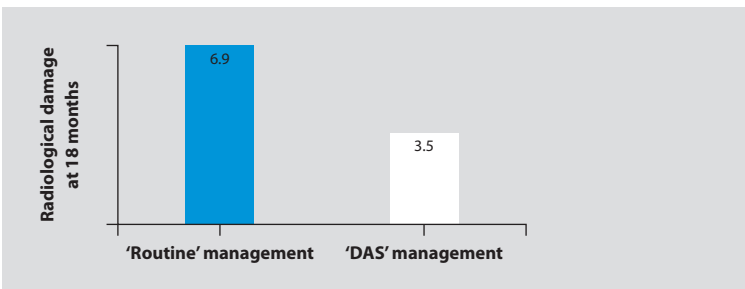

Figure 10.4 The TICORA trial demonstrated that treat-to-target ('tight-control') management yielded superior results to routine management in rheumatoid arthritis. These figures represent an increase in modified Sharp score, indicating radiographic joint damage. DAS, Disease Activity Score. Adapted with permission from © Elsevier, 2004. All rights reserved. Grigor et al [33].

into the pathogenic pathways of RA are still evolving, novel technologies continue to emerge, and there is still an important need for better therapies. On the other hand, we have come a long way and although some patients still require better treatments, for many others the currently available agents are sufficient to achieve stable disease control. This reduces the economic incentive for therapeutic innovations and perhaps also the enthusiasm of those working in the field. Moreover, trends in healthcare towards cost containment and an increasingly prohibitive clinical trial environment are strong forces that are slowing therapeutic developments. Increasingly, innovation will have to be generated in large partnerships between academia, industry, and regulators where considerations of efficacy, safety, and innovation will have to be linked to defensible long-term pharmacoeconomic prospects. A valid concern that must be recognized is that medical advances are held to much higher standards of cost-effectiveness than other expenditures that societies freely engage in. As an example, it is not at all clear that spending billions on hosting the Olympic Games generates quality-adjusted life-years at the same level that is required for medications. While the United States has seen large increases in healthcare spending that were not paralleled by commensurate improvements in health, in European societies a serious discussion may be needed on whether an overall healthcare expenditure of only 10% or so of gross domestic product is reasonable when health is arguably the most precious resource we possess.

Thus, the treatment of RA has seen tremendous advances but many challenges still exist. The task for both the researcher and the clinician is not only to find new potential treatments but also to ensure that the available treatments are used in an optimal manner and that patients suffering from RA receive the best possible care today, even as new developments make it virtually certain that better therapies will become available for the treatment of this important disease tomorrow.

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