

Rheumatoid arthritis and the evolution of therapy: from symptomatic to bench-to-bedside biological drugs

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Although treatment of rheumatoid arthritis was formerly based on the use of classical drugs, which admittedly had proved their efficacy in controlling the disease but whose exact mechanism of action remained unclear (or unknown), recent impressive advances in basic research on rheumatoid arthritis physiopathology have been made, leading directly to science-driven therapy of high specificity. In addition, an increasing number of potential targets are gradually being discovered, with subsequent engineering of – potentially therapeutic – interfering molecules. Beside the actually widely used tumor necrosis factor-blocking drugs, numerous treatments were thus developed, which focus on various levels of the complex immune process perpetuating the disease. If current clinical practice already allows the practitioner to choose between several highly efficient drugs, the exponential development of alternative therapies may complicate the decision, but should also transform long-term prognosis of these patients.

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease of unknown etiology, affecting approximately 0.5–1% of the worldwide population (approximately 100 million individuals). The disease, characterized by a usually symmetric inflammation of peripheral synovial joints and cervical spine, leads to early progressive erosion of cartilage and bone and, thus, subsequent disability. Until recently, traditional therapy of RA aimed at reducing patients' inflammation and symptoms with so-called classical disease-modifying antirheumatic drugs (DMARDs). The mechanism of action of these widely used drugs, despite many years of study and application, often remained unknown. Over recent years on the other hand, because of a better understanding and knowledge of subjacent immunopathology, impressive advances have been made in biologic therapy of RA. Indeed, new drugs are the direct targeted application of laboratory research and findings regarding involved cells and cytokines, introducing a far more specific and efficient way of treating this complex disease (Figure 1). We now have plenty of potential biologic therapies and it is necessary to find out what they tell us about the physiopathology of RA and how to choose them according to the clinical characteristics of the disease.

Actual biological therapies in RA:
following advances of basic science
Owing to its epidemiologic association with human leukocyte antigen-DR4, and elevated levels of major histocompatibility complex

(MHC) molecules and T lymphocytes found in inflamed synovium [1,2], RA was classically considered a predominantly, when not exclusively, T-cell-mediated disease. Despite the old hypothesis of B-cell involvement in the physiopathology (since the discovery of rheumatoid factor in the 1950s), this potential role was only entirely admitted owing to the recent demonstration of specific anti-B-cell therapy (rituximab) efficacy in RA [3–5]. Moreover, identification of close-range protein mediators, termed cytokines, increased rapidly during the 1980s, first with interferon molecules [6], interleukin (IL)-1 [7] and -2 [8], followed by tumor necrosis factor (TNF) [9] and lymphotoxin [10], gradually adding potential targets and producing new specific drugs.

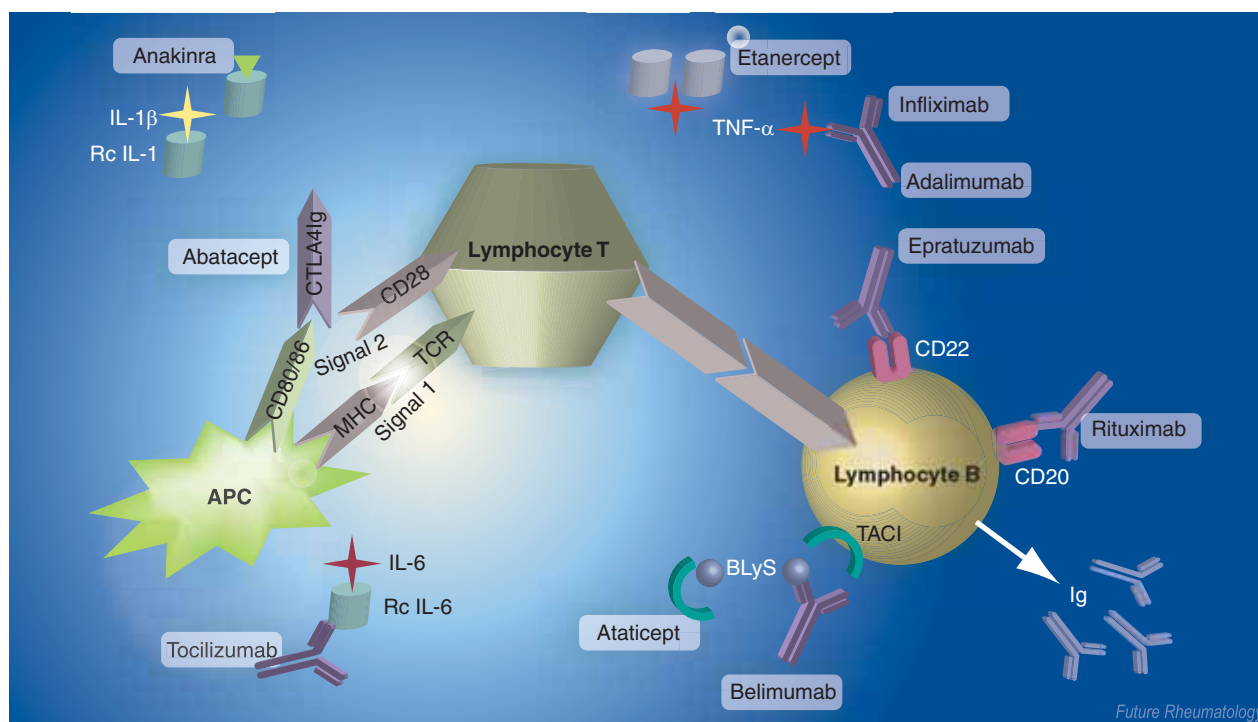
TNF- α inhibitors

TNF- α , a pivotal inflammatory cytokine released by activated macrophages, monocytes and T lymphocytes, was the first targeted molecule [11]. Three anti-TNF- α drugs are currently available, differing in method of administration and constitution, but all inhibiting the inflammatory cascade by blocking TNF- α before it binds to receptors on target cells. Infliximab is a chimeric (human/murine) immunoglobulin (Ig)G1 monoclonal antibody that binds soluble and membrane-bound TNF- α . It is given by intravenous infusion every 8 weeks after three closer induction administrations at weeks 0, 2 and 6, at a usual starting dosage of 3 mg/kg. Etanercept is a soluble, fully human, TNF- α receptor fusion

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Figure 1. Summary of pathophysiologic process in rheumatoid arthritis showing targets of main current biotherapies.



APC: Antigen-presenting cell; BLYS: B-lymphocyte stimulator; CTLA: Cytotoxic T lymphocyte-associated antigen; Ig: Immunoglobulin; IL: Interleukin; MHC: Major histocompatibility complex; TACI: Transmembrane activator and calcium modulator and cyclophilin ligand interactor; TCR: T-cell receptor; TNF- α : Tumor necrosis factor.

protein that is administered by subcutaneous injection. It can be dosed 25 mg twice-weekly or 50 mg once-weekly. Adalimumab is a recombinant human IgG1 monoclonal antibody that should be administered by subcutaneous injection at a dosage of 40 mg every other week. All of these three licensed anti-TNF- α drugs have shown an early onset of action (1–4 weeks), and a substantial symptomatic and structural efficacy in patients with early or established RA. Novel agents targeting TNF- α are also being developed: certolizumab (CDP-870) is a new agent that employs the prokaryotic expression of TNF-specific Fab antibody fragments, coupled to polyethylene glycol, resulting in a drug that can be administered by monthly subcutaneous injection. Golimumab (CNTO 148), another human monoclonal antibody to TNF- α that can also be used as monthly subcutaneous injections, was recently tested in patients with active disease despite treatment with methotrexate (MTX): after 12 months of treatment, significant reduction of signs and symptoms were observed, with no unexpected safety concerns [12].

IL-1 blockade

IL-1 is an inflammatory cytokine involved in a complex signaling system. By inducing the relapse of matrix metalloproteinases from chondrocytes and fibroblasts, it is implicated in the structural damage in RA [13]. Anakinra, a recombinant form of human IL-1 receptor antagonist that blocks the type I IL-1 receptor, has shown a significant superiority over placebo in controlling symptoms and slowing radiographic progression in RA patients [14–18]. However, its modest results compared with anti-TNF- α drugs and the need for daily subcutaneous injections often make this drug a substitution therapy.

Anti-CD20 monoclonal antibodies

Targeting CD20, a B-cell-specific antigen, is a novel alternative, aiming at controlling the inflammatory immune cascade of RA. This goal was achieved thanks to the genetic engineering of rituximab, a chimeric (human/murine) monoclonal antibody in the field of B-cell malignancies. Its intravenous administration in RA patients leads to selective B-cell depletion and

significant clinical improvement [19–21], and first results regarding radiographic outcomes look promising [19]: when given to patients with inadequate response to MTX, rituximab, in combination with MTX or with cyclophosphamide, resulted in more major clinical responses than MTX alone [21]. Further trials tested whether the adjunction of steroids (which was systematic in the previous study) may play a role in the results. Emery and colleagues demonstrated that methylprednisolone treatment preceding rituximab significantly reduced infusion-related adverse events after the first infusion, whereas no significant difference in efficacy could be observed between patients receiving steroids or placebo together with rituximab and MTX [20]. Moreover, Cohen and colleagues conducted a trial including only patients with inadequate response to anti-TNF therapy (which was the case for a third of the patients from the former study), and they were able to obtain significantly higher clinical improvement after 24 weeks with MTX in combination with two rituximab infusions only (administered at days 1 and 15), as compared with MTX and placebo infusions [19]. Because of possible immediate adverse reactions after infusion of this chimeric antibody rituximab, several fully human anti-CD20 antibodies were recently developed aiming at better tolerance, and the results of the first-phase trials using one of those (HuMax-CD20 human IgG1 monoclonal antibody [2F2]) provide interesting results on tolerance and efficacy in patients with follicular lymphoma [22].

Cytotoxic T lymphocyte-associated antigen 4-Ig (Abatacept)

Because activation of T cells by antigen-presenting cells requires two distinct signals (binding of T-cell receptor–MHC II-peptide complex and cell-surface costimulatory molecules [23]), a different way to inhibit the inflammatory immune cascade at an early phase consists of blocking these costimulation interactions. Abatacept is a soluble fusion protein (cytotoxic T-lymphocyte-associated antigen 4 fused to the heavy chain constant region of human IgG1) that is able to bind to CD80 and CD86 on antigen-presenting cells before they (co)activate CD28 on T cells. This drug, used as monthly 30-min infusion after an induction phase of three infusions every other week, has shown its superiority over placebo in improving symptoms of RA. In patients who had an inadequate response to MTX, addition of abatacept to MTX resulted in significantly higher

clinical benefits after 1 year when compared with a combination of MTX and placebo [24]. The subsequent open-label extension led to sustained clinical and radiographic results over 2 years, as well as comparable clinical improvement in patients initially treated with placebo [25,26]. Abatacept was also shown to reduce signs and symptoms of RA patients who had an inadequate response to anti-TNF therapy (our current best standard-of-care) [27], making it a promising treatment and an encouraging example for this new class of molecules. Combination of abatacept with another biologic therapy should, however, be avoided, because a specific study of patient's ability to tolerate concomitant treatment with abatacept and another DMARD showed an increased rate of serious adverse events in the subgroup of patients receiving a biologic background therapy [28].

IL-6 blockade

IL-6 is a pleiotropic cytokine with multiple physiologic and physiopathologic activities. A deregulated overexpression of IL-6 is responsible for inflammatory clinical and biological manifestations in patients with RA, such as an increased hepatic production of acute-phase reactants (C-reactive protein [CRP], fibrinogen or α -1 antitrypsin), B-cell activation, hyper- γ -globulinemia and antibody secretion, including rheumatoid factor (RF). Fatigue and fever in RA patients are also related with an abnormal level of IL-6. Tocilizumab (currently known as MRA) is a humanized anti-human IL-6 receptor monoclonal antibody that specifically inhibits the actions of IL-6. When administered intravenously – every 4 weeks – in two controlled trials [29,30], it demonstrated a significant improvement in disease clinical activity and biologic findings (hemoglobin level, platelet count, CRP, fibrinogen and RF), with a clear dose-dependent response. At 3 months, 78% of patients in the 8 mg/kg body weight group and 57% in the 4 mg/kg group achieved at least 20% improvement in disease activity according to the American College of Rheumatology criteria (ACR20), compared with only 11% in the placebo group. The even more stringent outcome, requiring at least 50% improvement (ACR50), was also fulfilled by 40% of the patients in the 8 mg/kg group (1.9% in the placebo group) [29]. Similar results were observed in the second trial, in which patients had previously shown an inadequate response to MTX: higher doses of tocilizumab led to better control

of disease activity, and combination with MTX was even more efficient (with, however, two cases of sepsis among the 50 patients in the group treated with the highest doses of tocilizumab) [30]. Additional clinical studies aiming to confirm the efficiency of this drug in combination with any other DMARD, as well as in the case of inadequate response to anti-TNF- α drugs, are imminent.

Actual guidelines for management of RA treatment

Several international groups have developed guidelines concerning the use of these new drugs in patients with RA, especially for TNF- α - and IL-1-blocking drugs [31–33]. In summary, patients diagnosed with RA (or with clear potential evolution towards the disease in cases of early arthritis) must first be started as early as possible on a conventional drug (DMARD), with MTX widely considered to be the anchor drug of this latter category of treatment, in addition to the usual complementary therapy, such as analgesics, nonsteroidal anti-inflammatory drugs or transient steroids (intra-articular, intramuscular and oral). There is also increasing evidence that use of a combination of two or three conventional DMARDs should also be considered, especially in severe disease or in the case of insufficient therapeutic response. Second, introduction of targeted therapies must be discussed in patients with active disease despite these first-line therapies. Definition of persistent activity and treatment failure is then based on clinical, biological and radiological evaluation after a sufficient follow-up time, but precise determination of activity can either be based on predefined cut-offs or the clinical opinion of the rheumatologist only. TNF- α -blocking drugs are usually considered a first choice, founded on earlier worldwide routine prescription and large observations. As no clinical trial compared one of the three available drugs with another, choice is usually based on patients' convenience for route of administration, access to treatment or practitioners' habits.

What then in the case of a lack of response to an anti-TNF- α drug, or drug-related toxic effects? Switching TNF- α -blocking therapy with either one of the two remaining available anti-TNF- α drugs [34–39] or with rituximab [40,41] can be considered, in that these options have both been successfully tested. Combination of anti-TNF- α drugs with other biotherapies, on the other hand, should be avoided because of the

increased risk of serious infections that was found when adding anakinra or abatacept. Regarding other therapies, such as the IL-1-blocking drug anakinra, their less impressive clinical results usually make them a substitution treatment for patients with serious adverse events or contraindications to reference drugs.

Newly discovered targets?

New potential biotherapies

Presented with the possibility to neutralize a protein using a monoclonal antibody or natural (or constructed) soluble receptor, every protein that demonstrates a potential implication in RA physiopathology is a potential target, even though its eventual use in clinical practice is also highly dependent on its tolerance, which remains an unpredictable characteristic requiring gradual testing. This article is not exhaustive, but will list the potential targets that appear to be important in the near future.

Targeting cytokines, adhesion molecules & chemokines

Cytokines

Several IL inhibitors targeting pro-inflammatory cytokines, such as IL-15, -17 and -18, are or will be tested in clinical trials. Some cytokines involved in bone destruction are likely very important, since many drugs are able to control inflammation but few can slow down or stop joint destruction in the manner of anti-TNF- α . One of the monoclonal antibodies of particular interest is the denosumab targeting the cytokine receptor activator of nuclear factor κ (RANK)-B. RANK/RANK ligand (RANKL)/osteoprotegerin is a complex system involved in the control of balanced action of osteoblasts and osteoclasts, and thus plays a major role in osteoporosis and also in RA, which is characterized by erosion of joints and global loss of bone mineral density. Denosumab is a monoclonal antibody inhibiting RANKL that has demonstrated efficacy in postmenopausal osteoporosis [42]. When administered in RA patients (by subcutaneous injection every 6 months), it effected a decrease in progression of erosions at 6 months as determined by magnetic resonance imaging (MRI), without evidence for any clinical effect, however [43]. The interest of this biologic agent will be this capacity to inhibit joint destruction. Indeed, this biologic agent could be used in association with other drugs (DMARDs or biologics) that efficiently control inflammation but do not limit joint destruction.

Adhesion molecules

Intercellular adhesion molecule (ICAM)-1 was another potentially interesting target for biotherapy in RA. However, although encouraging results could be observed after an initial course of murine monoclonal antibody to this molecule [44], repeat treatment was associated with adverse effects, suggestive of immune complex formation and poor clinical efficacy [45], and further development was consequently discontinued.

Chemokines

Chemokines and chemokine receptors are molecules involved in leukocyte migration into inflamed tissues (such as RA synovium) and are thus another potential target of biotherapies. CCL2/monocyte chemoattractant protein (MCP)-1 is one of these chemokines, believed to play a key role in this disease. A specific monoclonal antibody (ABN912) directed against CCL2/MCP-1 was developed and tested in a randomized, placebo-controlled, dose-escalation clinical trial [46]. However, although a very high dose-related increase in ABN912-complexed total CCL2/MCP-1 in peripheral blood of patients could be observed (up to 2000-fold), no clinical efficacy nor change in the levels of biomarkers in blood or synovial tissue (obtained by arthroscopic biopsy) could be shown. This apparently paradoxical increase of targeted molecules in the blood of patients receiving a specific antibody against that particular molecule can be explained by a displacement of CCL2/MCP-1 from its binding sites (on the extracellular matrix or erythrocytes) to the vascular compartment, due to a higher affinity of the monoclonal antibody compared with the 'natural' receptors. Again, this kind of finding confirms that the transition from basic science to clinical medicine is not a consistently natural process.

Another chemokine system, CCR1, a molecule found in RA synovial tissue, mainly on macrophages, was also investigated as a potential therapeutic target: an oral CCR1-antagonist, or placebo, was administered to RA patients, and clinical evaluation, as well as synovial biopsy specimens were obtained at days 1 and 15. Tolerance was good, with no serious adverse events reported and all 16 patients having completed the study. As expected, a significant decrease in macrophages and CCR1⁺ cells was observed in the synovium of patients treated with the antagonist compared with the placebo. The clinical efficiency was in favor of the active drug, with a trend towards clinical improvement,

although a definite conclusion could not be made because of the limited number of patients included in this Phase Ib trial [47].

Targeting cells survival: other B-cell- targeted therapies

Molecules regulating B-cell maturation, proliferation and survival are another potential target of specific biotherapy. B-lymphocyte stimulator (BLyS) – also known in the literature as *zTNF4*, *BAFF*, *TALL-1* and *THANK* – is a soluble cytokine produced by monocytes and dendritic cells that can activate B lymphocytes after binding to one of its specific receptors termed transmembrane activator and calcium-modulator and cyclophilin ligand-interactor (TACI), B-cell maturation antigen (BCMA) and BAFF-R (for B-cell-activating factor belonging to the TNF family). A second growth factor, a proliferation-inducing ligand (APRIL), which is able to bind TACI and BCMA only, was also shown to play a role in RA pathogenesis. Research for drugs targeting this new family of molecules led to development of belimumab, an anti-BLyS monoclonal antibody, and TACI-Ig (also called atacept), a recombinant fusion protein containing the extracellular, ligand-binding portion of the receptor TACI and an Fc portion of human IgG. Belimumab is a direct inhibitor of BLyS, while TACI-Ig acts as a soluble receptor of BLyS and APRIL. Their use in RA patients in Phase I and II clinical trials showed acceptable tolerance and potential effectiveness, which needs to be further explored in ongoing trials [48–50].

Targeting signaling pathways

Transmission of an intercellular signal towards cell nucleus is the next step in cell activation after an external messenger (e.g., a cytokine) has bound its membranous receptor. This intracellular pathway requires consecutive phosphorylations of enzymes termed protein kinases, which finally activate transcription factors, thus controlling the genetic expression of specific proteins (pro-inflammatory mediators, for instance). Numerous signaling pathways, including their respective activators and inhibitors, are currently known and more are periodically discovered, but four are presently considered especially relevant in RA pathophysiology: the TNF receptor-associated factor (TRAF)/I κ BK/nuclear factor (NF)- κ B, the mitogen activated protein kinases (MAPK) pathway, the phosphoinositide-3 kinase pathway and the janus kinases (JAK)/signal transducers and activators of transcription (STAT) pathway. The

particular interest seen in this part of basic research is easily explained by the fact that those pathways are the direct connection between famous cytokines involved in RA and expression of inflammatory mediators: NF- κ B, for instance, is activated by pro-inflammatory molecules, such as TNF- α or IL-1 β , and the generated cascade controls the genetic expression of important mediators, such as IL-1, IL-6, TNF- α , adhesion molecules or chemokines. It has even been considered the Holy Grail for RA. These signaling pathways can theoretically be controlled by various means: direct pharmacologic inhibition of the protein phosphorylation involved in the pathway, increase of expression of a natural inhibitor of the pathway, or root blockade of genetic expression of transcription factors or signaling molecules by antisense oligonucleotides.

Several synthetic p38 MAPK inhibitors, with demonstrated protective action in animal models of arthritis, have been developed, but none have yet passed early clinical trials in RA because of safety concerns, again highlighting the difficulty in combining outstanding efficiency with an acceptable tolerability and safety profile. Recently, a double-blind, placebo-controlled trial has shown promising results in RA patients with an inadequate response to MTX or anti-TNF drugs with CP-690,550, an orally active selective inhibitor of JAK3 [51].

Other concepts

Gene therapy

Transferring genes with potential therapeutic effects into synovium cells is another way of handling the disease at its origin. Indeed, induced intra-articular synthesis of therapeutic proteins could thus allow sustained, local control of inflammation while limiting side effects caused by the usual systemic route of administration of drugs. This can be performed because of nonviral or viral vectors (HIV-derived and adeno-associated virus being the most commonly used), but the modest transduction of synovium, the cost and complexity of their engineering and the potential unknown long-term consequences make it an attractive, but so far somewhat visionary, technique. This approach appears to be more adapted to hereditary (recessive or dominant) disease and is difficult to use in RA.

Small RNA inhibitors

Instead of targeting excreted noxious cytokines involved in RA, an attractive way of inhibiting the inflammatory process could be to block their

root production in the cell. This can be performed thanks to so-called small RNA inhibitors (sRNAi), consisting of endogenous or exogenous double-stranded RNA oligonucleotides that link and thus silence chosen complementary messenger RNA implicated in the disease in a highly specific manner. Unfortunately, these large and highly charged molecules can hardly enter cells and the actual experiments, so far carried out on mice, require electroporation of plasmids after intra-articular delivery. Experiments using electroporated sRNAi against murine TNF showed effectiveness in mice with collagen-induced arthritis when compared with saline solution or sRNAi targeting other uninvolved genes [52].

Induction of apoptosis: synoviocytes

The aggressive front of synovial tissue, termed pannus, invades and destroys local articular structure. The pannus is characterized by synovial hyperplasia, mainly composed of fibroblast-like synoviocytes (FLS) combined with a massive infiltration of lymphocytes and macrophages. Both increased proliferation and/or insufficient apoptosis might contribute to the expansion of RA FLS and several reports suggest inducing apoptosis of RA FLS as a therapeutic approach [53]. As RA FLS exhibit certain tumor-like features, we have investigated the effect of TNF-related apoptosis inducing ligand (TRAIL) on RA FLS survival. We have described that TRAIL induces apoptosis only in a subset of RA FLS that is followed by an induction of proliferation in the surviving cells [54]. This observation concurs with the previously reported pleiotropic responses of TRAIL in primary human tumor cells [55,56]. A similar finding was observed for another pro-apoptotic cytokine FasL, especially in the presence of pro-inflammatory cytokines demonstrating that in certain conditions, RA FLS are refractory to pro-apoptotic signals [57]. Modulation by pro-inflammatory cytokines of Fas/FasL-mediated apoptotic cell death of synovial cells in patients with RA. These findings challenge the proposed strategy to use TRAIL for targeting hyperproliferative cells. Sensitizing hyperproliferative cells for TRAIL-induced apoptosis by blocking the proliferative-signaling pathways has been suggested to overcome this problem. For this, it is essential to characterize the respective pathways triggered by TRAIL. Currently, however, there is no pro-apoptotic drug available in the treatment of RA, but this field deserves to be investigated because of the central role of RA FLS in inflammation and joint destruction observed in RA.

Mesenchymal stem cells & repair of bone & cartilage

Because mesenchymal stem cells (MSCs) are pluripotent adult cells with an ability to differentiate into most, if not all, musculoskeletal tissues [58], their potential use in repair and regeneration of damaged joints is of major interest. While they were originally discovered and described in bone-marrow tissue, other organs have thereafter been shown to be potential sources of MSCs, such as muscle or adipose tissue, and their introduction in bone defects, provided that they were previously genetically modified, enhanced repair of surgically created lesions in animal long bones and crania. Important research is also devoted to the repair of cartilage, usually employing chondroprogenitor cells mixed with vectors carrying chondrogenic genes [59].

In conclusion, we are experiencing a revolution in the treatment of RA. The number of new treatments available in this disease increases constantly, with almost one novel drug every year since 2001. The strategy used in RA will also likely change in the near future, with an

early use of biologic agents and particularly anti-TNF- α . The place of the other new biologic agents will have to be defined. It appears difficult to use a combination of two biologic agents implicated in inflammation or immunity because of an increased risk of infection. However, the combination of a drug with an efficacy on inflammation and another biologic preventing joint damage appears to be more realistic; although, we still have to be cautious with these new drugs. Indeed, the unfortunate events observed in a Phase I clinical study using an anti-CD28 monoclonal antibody (TGN1412), which led to major adverse reactions and intensive cardiopulmonary support in all six treated volunteers [60], reminds us that manipulating drugs targeting the immune system may be dangerous.

Future perspective

New biologic agents will be available in the coming years. Anti-TNF drugs place the barrier high because of their capacities to control both inflammation and joint destruction. In the future, actual guidelines for treatment of RA may change. Indeed, to stick to the concept of early and aggressive therapy in order to prevent joint damage, anti-TNF drugs might be used as first-line therapy. However, because of the high cost of these drugs, this strategy might be reserved for patients with polyarthritis associated with RA immunologic signature (rheumatoid factor and/or anti-CCP) or destructive features evaluated on x-rays or more advanced radiologic tools, such as ultrasound or MRI. Another alternative is to use anti-TNF drugs as first-line therapy in RA and possible RA, but for a short time (6 months) before stopping it. This strategy has been used in the Behandel Strategieën (BeSt) study, with more than 50% of patients still with a low disease activity after anti-TNF discontinuation [61]. A significant number of new biologics will be available in the coming years. These new biologic agents will have to demonstrate at least a similar efficacy and tolerability in order to replace anti-TNF as the first-line biologic proposed in RA. Based on the first clinical trials, the efficacy of new biologic agents on joint destruction appears to be less important. Therefore, for patients resistant or with a contraindication to anti-TNF drugs, it would be realistic to use a combination of biologic agents active on inflammation (i.e., rituximab or abatacept) with other biologics efficient on joint destruction (i.e., denosumab).

Executive summary

- Rheumatoid arthritis (RA) as a disease of major potential therapeutic interest:
 - High prevalence of the disease (~0.5–1% of the world population)
 - Severe prognosis without treatment or with insufficient (classical) drugs
- RA as a prototype of immune-mediated disease:
 - Entire immune system involved in physiopathology
- RA as a prototype of understanding of the disease:
 - Major worldwide scientific interest in RA basic science
 - Increased knowledge about the basic processes involved in the disease
 - Relevant animal models available
- Recent major advances in RA therapy:
 - Direct application of basic science findings in clinical practice: highly efficient drugs based on targeted therapy (from bench-to-bedside)
 - Progressive increase in number of available drugs in the last decade
 - Increased complexity in management of RA patients
- Infinite new potential targets of treatments owing to exponential discoverings in RA physiopathology
- Active clinical research in RA
 - Ongoing trials in every phase of clinical research (from 1 to 4)
- Ongoing research examining the potential application of brand new fields in medical therapy:
 - Gene therapy
 - Small RNA inhibitors
 - Induction of apoptosis
 - Mesenchymal stem cells and repair of damage

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