Review

Rheumatoid arthritis: What is refractory disease and how to manage it?

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Abstract

Despite the enthusiastic progresses in the field of rheumatoid arthritis pharmacotherapy the presence of prognostic factors associated with an unfavorable outcome and the inappropriate and/or delayed initiation of DMARDs can diminish the likelihood of achieving remission and increase the probability of refractoriness to treatment.

During the last decade we have experience exciting developments regarding the approval of new treatment options but few patients are reaching sustained remission and refractory patients continue to be a problem. Thus, it is critical to understand how clinicians can decrease the risk of refractoriness by close monitoring disease activity, using well defined and accepted composite measures, and by early and optimized use of DMARDs, including biologics.

The goal of this review paper is to offer an evidence based roadmap to prevent and to deal with refractory RA.

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1. Introduction

Rheumatoid arthritis (RA) is still an incurable disease, but if patients are early diagnosed and adequately treated an increasing number of affected individuals are able to achieve a state where only mild or no symptoms persist, which, depending on the defined criteria might be classified as remission [1]. However, the presence of some disease characteristics associated with a worse prognosis and/or inappropriate and/or delayed treatment of this disease, leads to refractoriness to treatment and to progressive joint destruction, functional impairment and increased mortality. To decrease the risk of refractoriness it is crucial to early diagnose RA patients, monitor tightly with appropriate tools disease activity, using well defined and accepted composite measures, and by early and optimized use of DMARDs, including biologics.

The goal of this review paper is to offer an evidence based roadmap to prevent and to deal with refractory RA.
2. The ever changing concept of early disease

Back in the 1980s, the concept of early RA included disease duration of up to 5 years and the management strategy was based on the pyramid concept. Only patients with severe disease and joint destruction received effective disease modifying antirheumatic drugs (DMARDs) and this was due to the fact that RA was mostly viewed as a mild chronic disease, with joint damage and disability occurring very slowly and late in the disease course. With the increasing evidence of the efficacy of early RA treatment and the advent of the “window of opportunity” concept, this paradigm changed, and in the 1990s the early RA definition evolved into maximum disease duration of 12 to 24 months [2]. In fact, if left improperly treated, most of these patients develop significant joint damage during this period of time [3]. More recently, this critical early period has been progressively reduced to few weeks, as there is increasing evidence that very early patients (within the first 6–12 weeks) may have a distinct immunopathophysiologic process and that they will benefit from earlier intervention [4–8].

3. New rheumatoid arthritis classification criteria

According to the 1987 American College of Rheumatology (ACR) RA classification criteria, revised by Arnett et al., there has to be at least 4 out of 7 criteria to establish the diagnosis of RA [9]. Two of these seven criteria are related with damage and, in early disease, rheumatoid factor (RF) is frequently negative. Thus, it is not surprising that these criteria do not perform well in early disease. A systematic review of the literature showed that sensitivity and specificity of the 1987 ACR criteria in early RA were 77% (68% to 84%) and 77% (68% to 84%) respectively [10,11]. Taking into account the relevance of early diagnosis, new classification criteria for RA had to be developed. This was clearly an unmet medical need as many arthritis patients that were not fulfilling the 1987 criteria were in fact early RA cases and this misclassification could be hindering effective therapy and was surely affecting the way epidemiological studies and clinical trials were being designed and interpreted [12,13]. A major collaborative effort between the ACR and the European League Against Rheumatism (EULAR) was settled and this seminal paper was recently published, emphasizing a major issue in early arthritis management which is to probabilistically decide whether or not we are facing a persistent inflammatory activity and the symptoms reported by the patients are also relevant aspects for the global assessment of disease activity. In fact, this has been tried to be captured by composite measures of RA disease activity. Two composite measures are extensively studied and validated: the EULAR Disease Activity Score (DAS) and the ACR Core Data Set. The use of composite measures usually partially overcomes the problem of the heterogeneity of RA clinical and laboratorial manifestations. In fact, there are patients that have normal ESR and still maintain painful and swollen joints and develop erosions; others have essentially high ESR and/or CRP and scarce clinical manifestations but have a radiologic progression that is equally severe. Composite measures have been shown to have a closer relationship with radiographic progression than single measures. Besides, composite measures diminish the sample size needed in clinical trials to detect significant differences between groups [18].

The ACR Core Data Set includes three visual analogue scales (VAS) for the physician and patient global assessment of disease activity and for patient perception of pain, two joint counts (number of tender and swollen joint counts), one laboratory measure (CRP or ESR), a measure of function (usually the Health Assessment Questionnaire, HAQ), as well as a yearly measure of radiological damage [19]. Nevertheless, the ACR Core Data Set fails to numerically quantify disease activity. The DAS score was developed to meet this requirement. It is based on a mathematical formula that computes four variables: the Ritchie articular index, the 44 swollen joint count, ESR and VAS for patient global assessment of wellbeing, which can be used interchangeably with VAS for disease activity. In the absence of the VAS a three item DAS (DAS28 variables) can be calculated [18]. Later on a DAS28 was developed using the 28 joint count for both tenderness and swelling, simplifying the joint count [17]. Levels of DAS28 are somewhat higher than DAS values and this is reflected in the way results have to be clinically interpreted, as is the case of the definition of low disease activity and remission. Only the DAS28 CRP has been compared with the DAS28 using ESR. Some studies show equivalence between these two scores whereas others do not [20–22]. Other simplified scores were developed, such as the simplified disease activity index (SDAI) and the clinical disease activity index (CDAI). Despite being less used, the SDAI offers a very simplified approach (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)) and was included in the new remission criteria recently published [23,24].

5. Response criteria

Both EULAR and ACR developed response criteria. The ACR response criteria are based on the previously reviewed core set. ACR 20, 50 or 70 stands for the percentage of improvement in this core set. A response (at least 20, 50 or 70% improvement) must be observed on both joint counts, and at least in three out of the remaining five variables. The EULAR response criteria are based on the DAS or DAS28 and take into account both the variation and the absolute value. This response can be classified as “no response”, “moderate response” or “good response” [19,25]. A DAS28 “no response” corresponds to an improvement of ≤0.6 or, for those with an endpoint DAS28 >5.1, an improvement of ≤1.2. A “moderate response” is defined as an improvement of >0.6 and ≤1.2 with an endpoint DAS28 ≤5.1 or an improvement of >1.2 with an endpoint DAS28 of >3.2. A “good response” is reserved for patients attaining a DAS28 of ≤3.2 and an improvement of >1.2. Additionally,
reduce disease activity, control joint damage and prevent disability. Synthetic DMARDs should be started in all patients upon diagnosis to patients, such as genetic variability affecting DMARDs metabolism and/or other factors can play a role in the refractoriness of RA in individual patients. For highly refractory patients continuous low dose DMARDs [37]. For this reason it is recommended by EULAR task force, other synthetic DMARDs such as leflunomide and sulphasalazine are generally placed as alternatives to MTX monotherapy in case of intolerance or contraindications, while cyclosporine and gold have limited use mainly due to adverse effects. Antimalarial drugs even if able to lead to some improvement of disease manifestations are weak inhibitors of joint damage and should be used as monotherapy only in exceptionally mild cases, associated with gastrointestinal intolerance, changing to parental route should be tried [36]. Other synthetic DMARDs such as leflunomide and sulphasalazine are generally placed as alternatives to MTX monotherapy in case of intolerance or contraindications, while cyclosporine and gold have limited use mainly due to adverse effects. Antimalarial drugs even if able to lead to some improvement of disease manifestations are weak inhibitors of joint damage and should be used as monotherapy only in exceptionally mild cases, associated with gastrointestinal intolerance, changing to parental route should be tried [36].

Glucocorticoids have an unquestionable role as an adjuvant therapy to DMARDs, used ideally for short periods of time to reduce inflammation, as a bridging therapy at diagnosis or in refractory patients between switches, particularly when the next treatment option has a delayed onset of action. Additionally glucocorticoids have showed to slow radiographic progression and are therefore qualified as DMARDs [37]. For highly refractory patients continuous low dose glucocorticoids, in association with other DMARDs, can be considered.

8. Refractoriness to synthetic DMARDs. What to do next?

Although combining synthetic DMARDs in patients who do not respond to monotherapy has additional benefits demonstrated in some clinical trials, in daily clinical practice the effective response rate is limited by adverse effects and low compliance. Clearly the SWEFOT trial has helped us to understand that in early arthritis patients, the combination of MTX and infliximab is superior to the addition of SSZ and HCQ [38]. For this reason it is recommended by EULAR task force, that if predictors of poor outcome are present (RF, ACPA, high disease activity, early erosions), and patients are refractory to the first synthetic DMARD they should be started on a biologic DMARD [28]. Otherwise, in the absence of severity prognostic factors switching to another synthetic DMARD (or even to a combination of synthetic DMARDs) might be considered.

At the moment there are nine biologic therapies approved for RA treatment, targeting specific components of the immune system pathways, which were developed in a bench to bedside approach. All TNF inhibitors (infliximab, adalimumab, etanercept, golimumab and certolizumab) as well as abatacept and tocilizumab are approved by Food and Drugs Administration (FDA) and European Medicine Agency (EMA) for use in DMARDs refractory patients (including MTX). Rituximab at the moment is only approved after TNF inhibitors (TNFi) failure, although efficacy similar to abatacept and tocilizumab has been...
shown in DMARDs failures. Anakinra, also approved for RA treatment, is less efficacious than the other biologics and its use is therefore reserved for selected cases, particularly in the setting of autoinflammatory diseases [39].

The fact that TNFi were the first biologics to be approved and have been used in clinical practice for the last 10 year has allowed the gathering of solid data on efficacy and safety. This has contributed to the positioning of TNFi as the first biologics to be started after DMARDs failure [28]. However it is expected that, as biomarkers of response to therapy become more specific and reliable, namely at the individual level, biologic DMARDs will be selected through a more personalized approach.

Cytokine blocking agents targeting TNF such as infliximab, etanercept, adalimumab and more recently certolizumab and golimumab have clearly revolutionized the way moderate to severe RA is treated. Different TNFi exhibit similar efficacy, with an ACR20, ACR50 and ACR70 response attained, respectively, by around 60%, 40% and 20% of the exposed patients [40]. It is well recognized from large clinical trials that TNFi optimal effect is obtained if they are used in combination with MTX. It is also possible that leflunomide can similarly work synergistically but further studies are required [41,42]. Concomitant use of MTX reduces human anti-chimeric antibodies (HACA) and human anti-human antibodies (HAHA) production, minimizing immunogenicity and acute infusion reactions. Moreover, secondary failure to anti-TNF monoclonal antibodies, which is known to be at least in part dependent on the production of HACAs or HAHAs, can be diminished by adding MTX [43]. When initial suboptimal response or a secondary failure occurs during the use of infliximab increasing the dose (up to 10 mg/kg, but more commonly up to 5 mg/kg) and/or shortening the administrations interval (up to every 4 weeks, but more commonly up to 6 weeks) can help to overcome lack of efficacy in some cases and by this way, reduce refractoriness to infliximab [44].

Datasets from registries (e.g., British Society for Rheumatology Registry, Swedish Registry, German Registry) have highlighted a small but increased risk of serious infections in comparison with synthetic DMARDs which seem to be higher in the first 6 months of therapy. Furthermore patients are more prone to intracellular bacterial infections such as those caused by Mycobacterium tuberculosis and this risk is higher in antibody treated patients than in etanercept exposed individuals [45]. The implementation of preventing strategies has reduced the incidence of latent tuberculosis [46]. Other preventive strategies like influenza and pneumococcal vaccination, careful review of dental hygiene, early diagnosis and treatment of respiratory, urinary tract and skin infections can also contribute to a safer use of TNFi. All these prophylactic measures can lead to a higher TNFi retention rate and thus to a decrease in treatment refractoriness.

Recently, two new TNFi, golimumab and certolizumab, have become available [47,48]. Both were developed based on strategies aiming at reducing immunogenicity. Golimumab was created upon human TNF immunization of transgenic mice expressing human immunoglobulins, being so a fully human monoclonal antibody. Certolizumab is a humanized antibody without the Fc fragment, which was substituted by a pegylated tail. Golimumab in association with MTX is efficacious in MTX inadequate responders, TNFi failures and MTX naive patients. In phase III studies golimumab 100 mg was not superior to 50 mg subcutaneous, neither golimumab monotherapy 100 mg was superior to MTX alone, leading to a final approved regime of 50 mg subcutaneous once a month [49–52]. Certolizumab has showed efficacy in MTX (RAPID1 and RAPID2) and in DMARDs (FAST-4WARD) refractory patients [53–55]. Certolizumab has a quick onset of action and should be administrated according to an induction regime of 400 mg at 0, 2 and 4 weeks and 200 mg every two weeks thereby.

The addition to RA therapeutic armamentarium of two new potentially less immunogenic TNFi holds the promise of improving the chances of response at the individual level, contributing to minimizing refractory cases in clinical practice.

### 9. Refractoriness to TNF inhibitors. What to do next?

The percentage of patients for whom the first TNFi is inefficient (primary failure) has been estimated to be around 1/3 of the patients [56]. Furthermore, a significant percentage of patients will also lose efficacy latter on (secondary failure). For both these subgroups of patients different treatment options are now available, including switching to an alternative TNFi or changing to an agent with a different mechanism of action.

Switching to another TNFi is supported by arguments related to pharmacology, disease mechanisms and immunogenicity. First of all, TNFi differ in their half-lives and affinities and this might be translated into a different duration of TNF neutralization, leading to different response patterns in individual patients. In addition, in spite of similar efficacy in RA and Spondyloarthritides the differences in the mechanism of action between monoclonal antibodies and the TNF receptor fusion protein is reflected, for instance, in a low effect of etanercept in Crohn’s Disease and in other granulomatosis diseases, and this might be relevant in some nonresponding patients, given the individual heterogeneity of RA physiopathology. Finally, the appearance of neutralizing antibodies against monoclonal antibodies in nonresponding patients might be an extra argument for switching.

Therefore lost of efficacy to a TNFi can potentially be recaptured by switching to another TNFi. The response to a second TNFi has been reported to be slightly lower in comparison to TNFi naïve patients but it is clearly reduced with further switches [57]. Additionally, the reason for switch might also influence the outcome, with discontinuation due to adverse events and due to secondary failure being predictors of better response to a second TNFi than when the switch is made after a primary failure [57,58]. These data suggest that switching to a second TNFi can be considered, with the possible exception of primary failures. However, switching to another biologic with a different mechanism of action is clearly advisable if a second response failure occurs.

Our armamentarium and experience with the use of other biologics has markedly increased in recent years. Specifically, rituximab, tocilizumab and abatacept have proven their efficacy in anti-TNF refractory patients in large randomized clinical trials (RCT) [59–62].

The rational for the use of rituximab in the treatment of RA is based in the ability to reduce autoreactive antibodies synthesis, such as RF and ACPA, and impair antigen presentation to T cells, as well as cytokine production. Patients with inadequate response to TNFi can benefit from initiating B cell depleting therapies namely rituximab. Finckh et al. in a longitudinal cohort study have shown that the improvement of DAS28 score was better in patients that received rituximab after the failure of one TNFi than those who were switched to another TNFi [63]. When the reason for switching was considered in a later study it was demonstrated that the magnitude of DAS28 improvement between groups was higher in those who switched due to inefficacy of the TNFi comparing to those who changed due to other reasons [63,64]. Well known predictors of response to rituximab (RF and/or ACPA+) have to be taken into account in the selection of patients, even if a few patients who are not positive for RF or ACPA might also respond favorably [65]. Furthermore, experience with the use of rituximab has showed that retreatment might potentiate efficacy in responders and secondary loss of response is generally rare [66,67]. However, for primary failures to RTX, switching to a biologic DMARD targeting other immunologic pathways should be preferred. At the moment, retreatment using a “treat to target” strategy instead of an on-demand regime seems to be more effective but longer follow-ups are needed to clarify this issue and the possible requirements for a fixed schedule are being evaluated [68].
Encouraging data from five phase III RCT lead to the approval of tocilizumab both in the US (TNFi failures) and in Europe (DMARDs and TNFi failures), blocking the effect of the pleiotropic IL6 cytokine in RA patients is translated into similar efficacy to TNFi, regarding disease activity and radiographic progression and clear superiority to MTX [69]. The possibility of using tocilizumab as monotherapy in patients that are refractory or intolerant to MTX is a distinctive feature of this drug.

Abatacept is a soluble recombinant fully human protein comprises the extracellular domain of CTLA4 and the Fc portion of an IgG1 molecule that has been modified to prevent complement activation. The principle of its use in RA is dependent on the induction of T cell anergy by blocking the second signal between CD28 and CD80/86 necessary for T cell activation. Based in data from in vivo experiments it is assumed that abatacept develops its action by decreasing T cell activation, migration and secretion of cytokines [70]. Particularly, abatacept is able to reduce progression to RA in a subgroup of patients with undifferentiated/early rheumatoid arthritis, highlighting its efficacy in early treatment [71].

Despite the increased number of biologics available, until now there is not enough evidence that would help clinicians to position non-TNFi biologics according to disease phenotypes or to helpful specific biomarkers. Therefore, clinicians are still basing their decisions on personal experience and on the safety profile of each biologic drug.

10. Could biologics used as a first line therapy reduce refractoriness in rheumatoid arthritis?

The question if using biologic DMARDs as first line therapy early in the disease course could reduce refractoriness is still not clearly answered. Early intervention with biologic agents seems to offer a significant advantage in the magnitude of their benefits. TNFi including infliximab (Go-Before), etanercept (COMET), adalimumab (PREMIER), and golimumab (Go-Before) have proved that when used in early disease in MTX naïve patients they were superior to MTX in monotherapy, particularly in their capacity to arrest radiographic progression [49,72–74]. Similar results would be expected if certolizumab had been tested in this same population. Furthermore, recent analysis of the 4-year follow up of the BeSt study revealed that first line use of infliximab led to a more sustained remission as compared to patients that received this drug in latter stages of the treatment strategy [75]. Similarly, the SWEFOT study highlighted benefits from the combination of infliximab plus MTX in comparison with triple synthetic DMARDs therapy [38]. Recent data from a prospective open study suggests that although a faster reduction in DAS28 in patients starting MTX and adalimumab as first line treatment is observed at 12 weeks, the clinical and radiographic outcomes at 52 weeks did not differ from those who were changed to the same regime after 3 months, if they were refractory to MTX [76]. Therefore this data needs further analysis.

All current biologics (TNFi, tocilizumab, abatacept and rituximab) have increased benefits when used combined with MTX in DMARDs naïve patients [77–79].

Despite the ongoing discussion, at the moment there in not enough evidence to support generalized use of biologics in association with MTX as first line therapy. By doing so, we would be over treating at least 15% to 40% of patients who would respond to MTX monotherapy [80]. This approach can be however considered in selected cases, when clear unfavorable prognostic factors are present and disease activity is very high.

11. Refractoriness to approved therapies. What to do next?

Despite the efficacy and increased number of biologic therapies available it has been reported that the ACR70 response rate to a second biologic is of 5–15% and the DAS28 remission is reached by 9–15% of this patients, leaving the proposed treatment targets clearly unmet [81].

Many exciting new biological agents are in development for the treatment of RA. Inclusion of selected patients that became refractory to all approved biologics in ongoing clinical trials according to clinical judgment can bring potential benefits for disease control. For example new cytokine antagonists, namely blocking IL6, IL17 and GM-CSF are being studied [82–88]. Other anti-CD20 antibodies including the fully human ofatumumab and the humanized ocrelizumab and veltuzumab are in phase II/III trials [89–91]. Neutralization of the B cell survival and activation cytokines BLYS (or BAFF) and APRIL is an approach that is in development, despite the disappointing results obtained with atacicept (which blocks both BLYS and APRIL) and could therefore reversibly suppress B cell function across maturation stages. Signaling pathways including NF-κB and p38 MAPK pathways are being targeted by small molecules, as is also the case of JAK and Syk kinases [92,93]. Possible complementary approaches arresting the effects of inflammation in bone metabolism such as inhibiting osteoclast differentiation are particularly attractive [94].

The treatment potential of using stem cell transplantation (SCT) for severe refractory RA patients at risk of high mortality and previously to irreversible damage should not be forgotten. SCT is relatively well tolerated by most of the patients, with transplant related mortality after 100-days of 1% and a general survival of 94%. It is associated with improvement of disease activity and function and inhibition of joint destruction. Peripheral blood is the most commonly used source of stem cells and autologous transplant preferred. High doses of cyclophosphamide led to superior disease control than lower doses [95]. Relapses are however rather frequent with a progression-free rate of 23% at 3-year and 18% at 5 years and DMARDs such as MTX, cyclosporine and rituximab are required to maintain disease activity controlled [96]. Since the advent and broad use of biologic therapeutics SCT has indeed become less commonly used for RA treatment as compared to other rheumatic diseases, such as systemic sclerosis, reflecting the increase of treatment options, but it can still be considered as a salvage treatment.

Furthermore, mesenchymal stromal cells (MSC) have showed in vitro and in vivo anti-proliferative and anti-inflammatory properties that support the rational for their use in inflammatory arthritis [95]. MSC effects on collagen induced arthritis models have been contradictory, but their potential immunoregulatory effects might be translated into a valuable therapeutic approach [97].

12. Conclusions

Despite the enthusiastic progresses in the field of RA pharmacotherapy, few patients are reaching sustained remission and refractory patients continue to be a problem. However, we have the tools to perform at a higher level. We have now well defined and accepted composite measures for monitoring RA disease activity, consensus treatment targets, a managing strategy that has been progressively updated and a vast option of highly effective drugs. We should now put the emphasis on the human factor and assume that managing RA in the 21st century is a complex and highly differentiated task that put the emphasis on the human factor and assume that managing RA updated and a vast option of highly effective drugs. We should now put the emphasis on the human factor and assume that managing RA in the 21st century is a complex and highly differentiated task that should be taken care by specialized and externally certified centers, through a benchmark approach, where the best balance between efficacy, safety and costs will be required.

Take-home messages

• Refractoriness can be mitigated by early diagnose of RA patients, tight monitoring using appropriate tools to measure disease activity, identification of patients with worse prognosis and starting early and adequate treatment strategy aiming remission at each individual patient.
• In spite of the increased number of biologics available, until know there is not enough evidence that would help clinicians to position biologics according to disease phenotypes or to helpful specific biomarkers, therefore, clinicians are still basing their decisions on personal experience and on the safety profile of each biologic drug.


