OPTIMISING PATIENT OUTCOMES THROUGHOUT THE RHEUMATOID ARTHRITIS PATIENT JOURNEY: THE EXCEPTION, THE STANDARD, AND THE RULE

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Chairperson

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Speakers

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MEETING SUMMARY

Prof Peter Taylor opened the symposium focussed on optimisation of treatment for rheumatoid arthritis (RA) at each stage of the patient's journey. Prof Ronald van Vollenhoven reviewed the evidence for first-line biologics in the 'exceptional patient' and explored which patients may be suitable for such treatments. Prof Taylor then expanded on how use of such treatments could be optimised and when to introduce biologic therapy for the so-called 'standard' patient. Finally, Prof Daniel Aletaha discussed treatment options and targets for patients who have failed on a biologic as 'the rule' in the treatment of RA.

The Role of Biologics for Disease-Modifying Anti-Rheumatic Drugs in Naïve Patients: The Exception

Professor Ronald van Vollenhoven

Recommendations to encourage standardisation of RA treatment were issued by the European League Against Rheumatism (EULAR) in 2010 and revised in 2013. The 2013 EULAR recommendations discourage the immediate initiation of biological therapy in combination with methotrexate but do indicate that in an 'exceptional patient' this might nonetheless be justified.[1]

Initial treatment of RA after diagnosis is recommended to be with a disease-modifying anti-rheumatic drug (DMARD); specifically, a conventional DMARD, not a biologic (Figure 1). Challenging this approach are data from several trials which provide evidence that the combination of a biologic with methotrexate is superior to first-line treatment with methotrexate alone for early RA.

The ASPIRE study was one of the first to investigate first-line anti-tumour necrosis factor (TNF) therapy in early disease.[2] Addition of infliximab (at 3 or 6 mg/kg) to methotrexate resulted in robust improvements in American

College of Rheumatology (ACR) 70% response (ACR70) at 54 weeks (33% and 37% for infliximab 3 and 6 mg/kg, respectively, in combination with methotrexate, versus 21% for methotrexate alone; both p<0.001). This was also one of the first trials to show that anti-TNF therapy combined with methotrexate is one of the most effective ways to prevent radiological damage, with mean change from baseline in Sharp/van der Heijde score of 0.4 and 0.5 for infliximab 3 and 6 mg/kg, respectively, in combination with methotrexate, compared with 3.7 for methotrexate alone (both p<0.001).[2]

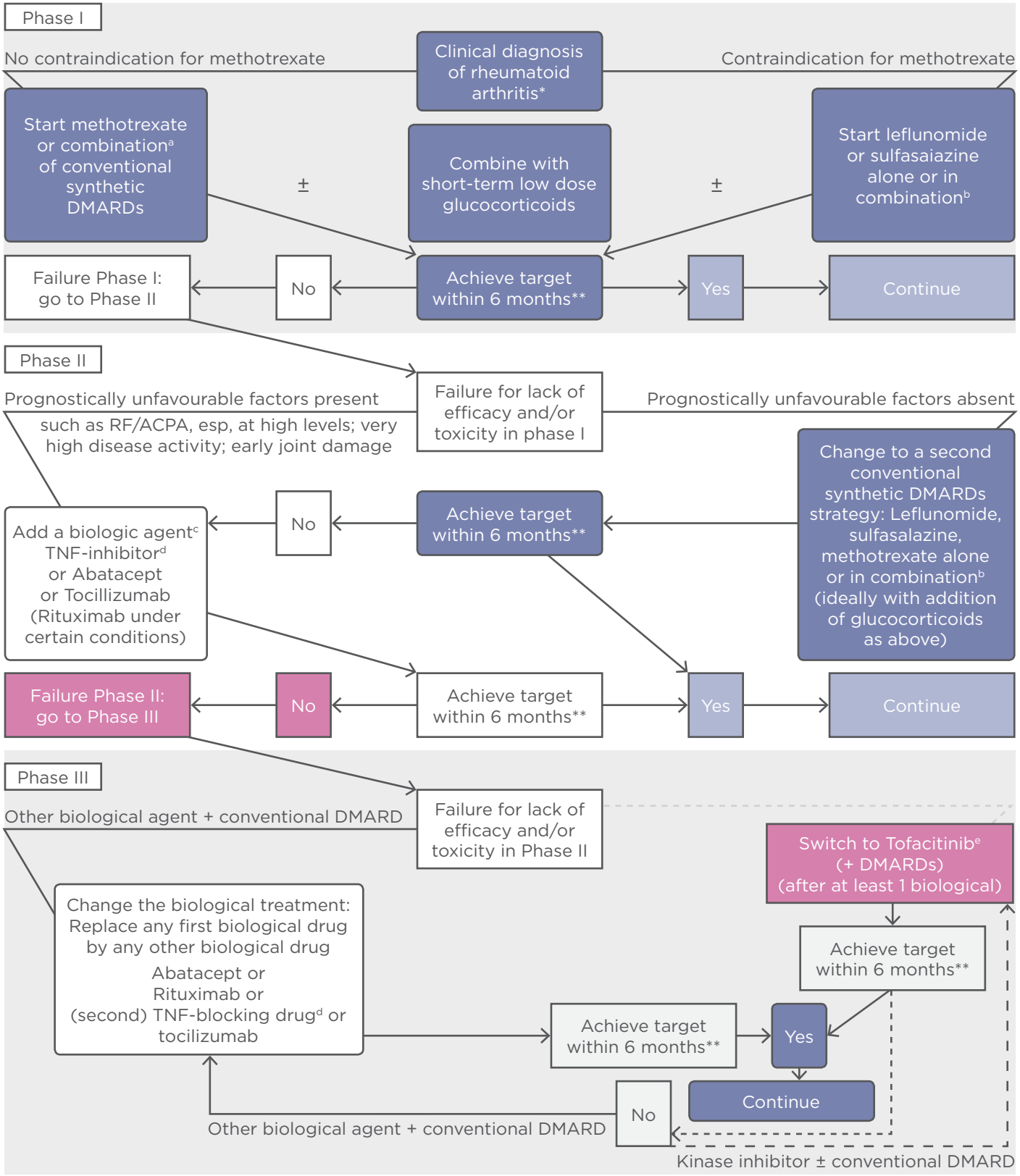

Figure 1: Treatment algorithm based on 2013 EULAR recommendations for rheumatoid arthritis management.

Figure 1 continued.

*2010 ACR-EULAR classification criteria can support early diagnosis.
**The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable at least low disease activity; the target should be reached within 6 months, but therapy should be adapted or changed if no improvement is seen after 3 months.
a) The most frequently used combination comprises methotrexate, sulfasalazine, and hydroxychloroquine;
b) Combinations of sulfasalazine or leflunomide except with methotrexate have not been well-studied, but may include combining these two and also with anti-malarials;
c) these circumstances are detailed in the text;
d) Adalimumab, certolizumab, etanercept, golimumab, infliximab, or respective well-studied and FDA/EMA-approved biosimilars;
e) where licensed.
Full black line: recommended, as shown; grey interrupted line: recommended for use after biologics failure (ideally two biologics failure); interrupted black line: recommended after two biologics failed but efficacy and safety after failure of abatacept, rituximab, and tocilizumab not sufficiently studied; black dotted line: possibly recommended but efficacy and safety of biological use after tofacitinib failure unknown at time of developing the 2013 update of the recommendations.
DMARDs: disease-modifying anti-rheumatic drugs; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; TNF: tumour necrosis factor; ACR-EULAR: American College of Rheumatology-European League Against Rheumatism; FDA: US Food and Drug Administration; EMA: European Medicines Agency.
Adapted from Smolen JS et al.[1]

The PREMIER study evaluated adalimumab with methotrexate compared with each treatment alone.[3] ACR70 was higher at 1 and 2 years for the combination (46% and 47%, respectively) than for methotrexate alone (28% at both time points). Again, the combination was more effective than monotherapy for preventing radiological damage.

In a further trial, comparing etanercept with methotrexate monotherapy, ACR70 was 19% and 29% for etanercept 10 and 25 mg, respectively, versus 24% for methotrexate alone at 2 years.[4] At this time point, 53% and 63% of patients treated with etanercept 10 mg and 25 mg, respectively, also had radiological non-progression (change in total sharp score [TSS] of <0.5 from baseline), versus 51% of patients treated with methotrexate monotherapy.

More recently, the C-EARLY trial evaluated certolizumab pegol + methotrexate compared with methotrexate alone.[5] The primary endpoint of sustained remission (defined as disease activity score [DAS]28-erythrocyte sedimentation rate [ESR] score <2.6 at both Week 40 and Week 52) showed statistically significant improvements with certolizumab + methotrexate versus methotrexate alone (28.9% versus 15%; odds ratio [OR]: 2.3; p<0.001). Furthermore, sustained low disease activity (LDA) (DAS28-ESR ≤3.2 at both Week 40 and Week 52) was significantly higher for certolizumab + methotrexate than for methotrexate alone (43.8% versus 28.6%; OR: 2.0; p<0.001), as was remission (DAS28-ESR <2.6) at Week 52 (42.6% versus 26.8%; OR: 2.0; p<0.001). The mean change from baseline in TSS was 0.2 for certolizumab + methotrexate versus 1.8 for methotrexate alone (p<0.001); the proportion of patients with radiological non-progression was markedly higher with the combination: 70.3% versus 49.7% for methotrexate alone (OR: 2.4; p<0.001).

A similar trial (C-OPERA) conducted in Japan showed consistent results at 1 year.[6] DAS28-ESR remission (score <2.6) rates were 57.2% for the combination certolizumab pegol + methotrexate versus 36.9% for methotrexate alone (p<0.001). Simple Disease Activity Index (SDAI)-based remission (score <3.3) rates were higher for the combination (57.9% versus 33.8%; p<0.001), as were Boolean-based remission (tender joint count ≤1 in 28 joints, swollen joint count ≤1 in 28 joints, C-reactive protein ≤1 mg/dL, and Patient's Global Assessment of Disease Activity ≤1) rates (45.3% versus 28.0%; p<0.01). The U-ACT-EARLY trial also showed comparable results combining tocilizumab with methotrexate.[7] The combination was superior in terms of sustained remission rates (DAS28 <2.6 and swollen joint count ≤4, sustained for ≥23 weeks with the exception of ≤2 visits at which DAS28 could be ≥2.6 but <3.2) which were 86% for the combination versus 44% for methotrexate alone.

Given the available evidence, it could be questioned why the combination of MTX and biologics is not routinely recommended in first-line therapy. Firstly, a combination strategy would clearly over-treat some patients (an estimated 30% of RA patients), since some would do well with monotherapy. Secondly, medical risks are greater for combined treatment, since each drug has its own potential side effects. Thirdly, and probably most importantly, there is a large cost difference between combination therapy and methotrexate monotherapy. Lastly, some studies have suggested that longer-term results may be equal if conventional DMARDs are started first and biologics added later. In the BeST trial, immediate treatment with infliximab + methotrexate showed better remission rates in the first year compared with immediate treatment with methotrexate + prednisone, sequential monotherapy, or step-up therapy.[8] But long-term outcomes over 7 years were similar, as patients in the other three groups could also receive methotrexate + anti-TNF therapy.

For these reasons, first-line biological therapy should not routinely be considered. Nonetheless, first-line biological might be considered for patients with high inflammatory burden, allowing rapid relief of symptoms, and for those at highest risk of irreversible radiological damage. It may also be considered for patients for whom the only other rapidly-acting alternatives, glucocorticoids, are contraindicated.

A potential future strategy is induction-maintenance therapy. The OPTIMA trial evaluated induction therapy with adalimumab + methotrexate or placebo + methotrexate followed by a continuation/withdrawal phase for patients achieving stable LDA after 26 weeks.[9] For patients who stopped adalimumab, remission rates (DAS28 <3.2) decreased only slightly. In Phase II of the C-OPERA study, patients initially treated with certolizumab + methotrexate received maintenance with methotrexate alone after 1 year.[10] At 2 years, SDAI-based remission rates remained higher in patients initially treated with the combination than in those initially treated with methotrexate alone (41.5% versus 29.3%; $p<0.05$), as did rates of radiological non-progression (84.2% versus 67.5%; $p<0.001$). In the PRIZE study, all patients received open-label etanercept + methotrexate for 52 weeks and were then randomised to etanercept + methotrexate, methotrexate alone, or placebo.[11] A lasting benefit in DAS28 remission was observed after biologic was stopped. The induction-maintenance strategy is also currently under investigation in the C-EARLY trial.

In conclusion, first-line use of biologics is not recommended for routine use, but may be an appropriate medical choice in exceptional cases. In the future, induction-maintenance using biologics as first-line therapy may prove to be a highly effective and cost-effective alternative to the current treatment paradigm, but further studies are needed.

When to Start Biologics: The 'Standard Patient'

Professor Peter Taylor

Both ACR and EULAR recognise the importance of regular assessment of patients, evaluating disease activity, treating appropriately, and escalating therapy when required, with a view to attaining the aspirational targets (remission or LDA).[1,12] Treating patients early with effective therapies achieves remarkably high and sustained remission rates. However, in the clinic, some patients will never achieve aspirational targets.

Detailed recommendations are available for optimising pharmacological therapy, but optimising the patient through lifestyle interventions or adaptation should also be considered. Phenotypic expression of RA has become less severe in recent decades, possibly because of reductions in smoking at the population level. An epidemiological study in an early RA cohort from Sweden showed that both current and past smokers are less likely to have good response either to methotrexate or TNF inhibition.[13] In the SWEFOT trial, smoking was a predictor of rapid radiographic progression at 1 year (Sharp/van der Heijde score increase ≥5) in DMARD-naïve RA patients treated with methotrexate, with an OR of 2.25 for current versus never smokers, and 2.67 for current versus non-smokers.[14] Smokers also have a greater likelihood for poor functional progression.[15] Therefore, patients should be advised not to smoke; given that RA has heritable components, this advice should also be extended to patients' children.

Obesity also has an effect on RA pathobiology and response to therapy. In a prospective study, overall quality of life measured by total Medical Outcomes Study short form 36 score was lower among obese

RA patients than in normal or overweight patients, as were physical and mental components.[16] Data from the Swedish cohort also showed that the likelihood of achieving LDA or EULAR good response at 6 months is lower for overweight or obese patients than patients of normal weight, with OR for LDA, EULAR good response and remission of 0.49, 0.50, and 0.58, respectively.[17] Therefore, advice about lifestyle issues (smoking and weight loss) is important, emphasising the role of the multidisciplinary team beyond pharmacological intervention.

EULAR recommends that methotrexate should be part of the first treatment strategy for patients with active RA.[1] Methotrexate is a highly effective agent, both as monotherapy and in combination with glucocorticoids, other conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs), and serves as an anchor drug in RA. As monotherapy with or without glucocorticoids, it is effective in DMARD-naïve patients and leads to LDA or ACR70 response in 25–50% of patients within 6–12 months. Early response is a strong indicator of sustained response. Emerging data from the C-EARLY study with optimised methotrexate (initiated at 10 mg/week and rapidly escalated to maximally tolerated dose) suggested that patients who fail to achieve a response (as little as DAS28 improvement of 0.6) by 12 weeks are unlikely to do well at 1 year.[18] Therefore, one might consider step-up treatment at an early time point of 3 months.

The CONCERTO study was a randomised, double-blind, parallel-armed study of methotrexate in combination with adalimumab to assess whether an increasing trend of efficacy and decreased safety exists when increasing methotrexate dose.[19] This study showed that doses of 10 or 20 mg/week in combination with the biologic confer equivalent benefit in terms of radiographic non-progression (change in modified TSS ≤0.5; 76.8% versus 77.6% of patients) and comprehensive disease control (defined as DAS28-C-reactive protein <2.6, Health Assessment Questionnaire-Disability Index <0.5, and change in modified TSS ≤0.5; 21.2% versus 26.5% of patients). Therefore, if a patient cannot tolerate escalation of methotrexate dose, it may be possible to continue methotrexate at a lower dose with nearly all the benefit.

Another issue with methotrexate is that bioavailability of oral treatment is not linear across the 10–25 mg dose range.[20] Subcutaneous methotrexate shows linear exposure, and has been associated with better treatment survival than with oral therapy, with treatment failure rates at 1 year of 49% and 77%, respectively (p<0.0001).[21]

Since methotrexate is a folic acid mimetic, concomitant folic acid should be given. Patient education is important, as folic acid supplementation is associated with better survival on methotrexate, adherence, and outcomes.[22] Benefits of folic acid supplementation also include a 26% relative risk reduction for gastrointestinal side effects (p=0.008), 76.9% relative risk reduction for serum transaminase elevation (p<0.00001), 60.8% relative risk reduction for withdrawal from methotrexate for any reason (p<0.00001), and 28% relative risk reduction for stomatitis (not significant).[23]

EULAR recommendations state that, in DMARD-naïve patients, csDMARD monotherapy or combination therapy of csDMARDs should be used, irrespective of the addition of glucocorticoids.[1] Several additional studies suggest that csDMARD combinations are superior to methotrexate monotherapy, with some showing efficacy to be similar to that of bDMARDs, suggesting that this could be a more cost-effective option. Although these trials yielded similar results, controversy persists because of the methodological limitations of these studies. Moreover, recent data suggest that sequential monotherapy is as effective as combination therapy in clinical, functional, and structural outcomes, and that stepping up from methotrexate monotherapy to a biological agent has significant superiority over a combination of csDMARDs.

The SWEFOT study showed a numerical, but not statistically significant, trend for higher EULAR good response with bDMARD (infliximab) + methotrexate than with csDMARD (sulfasalazine + hydroxychloroquine) + methotrexate among RA patients who failed methotrexate treatment (39% versus 25% at 12 months, 38% versus 29% at 18 months, 38% versus 31% at 24 months).[24] The RACAT study was a non-inferiority trial in which patients with active RA were randomised to triple therapy (sulfasalazine + hydroxychloroquine + methotrexate) or etanercept + methotrexate.[25] Patients who did not respond switched to the other therapy at 24 weeks. DAS28 remission (score ≤2.6) was 12.7% for triple therapy versus 21.7% for etanercept + methotrexate at 24 weeks (p=0.03), and 20.8% versus 25.2% at 48 weeks (not significant); ACR70 response was 5.0% versus

16.0% at 24 weeks (p=0.001) and 18.1% versus 26.5% at 48 weeks (p=0.08).

csDMARD combinations may be more efficacious than csDMARD monotherapy in early RA.[26] Escalating treatment from csDMARD monotherapy to combination therapy is effective in a high proportion of early RA patients.[24] This may be cheaper than escalation to bDMARD therapy and csDMARD combination therapy may be associated with a better tolerability profile than bDMARD therapy.

Current EULAR recommendations state that bDMARDs should be started when patients have not achieved the therapeutic target after treatment with csDMARDs for 6 months (or had no improvement at 3 months).[1] Although the armoury of effective drugs for RA has expanded significantly, particularly for biologics, the lack of head-to-head studies makes it difficult to choose between them.

In conclusion, with respect to the 'standard' patient, it is important to optimise the methotrexate dose and mode of delivery with a view to the ratios of benefit-to-risk to tolerability and persistence on the drug. Emerging data suggest that failure of clinical response to methotrexate by 3 months strongly predicts failure to achieve remission or LDA target with methotrexate at 1 year. Patients can be assisted to feel empowered to help themselves achieve the best response to therapy by optimising their weight and by smoking cessation. Simple education and reminders to take folic acid supplementation can help persistence on methotrexate and significantly reduce gastrointestinal toxicity and hepatotoxicity.

How to Optimise Biologics: The Rule

Professor Daniel Aletaha

Optimisation of treatment involves setting a clear target for response, creating a plan to assess progress and adjusting the approach when required.[1] When setting the target, we must first ask what the target should be. Remission criteria endorsed by ACR and EULAR (Table 1) involve two categories: full criteria for clinical trials, and adapted criteria for clinical practice (without acute phase reactants).[27,28] Within these, there are also two methods of determining remission: Boolean (which involves intersection of clinical criteria, all of which must be fulfilled) and index-based (which involves the sum of criteria, allowing compensation for one variable not being in remission if all other variables are).[29]

The critical target is the one that predicts for prevention of disease progression. The Boolean set of criteria was shown to have a positive likelihood ratio of good outcome of 2.9 if remission criteria are fulfilled, whereas the DAS28 <2.6 has a lower positive likelihood ratio of 1.0 for a good outcome, because patients with DAS28 response may still have swollen joints.[27] Decreasing the cut-off point for DAS28 to <2.0 slightly increases the positive likelihood ratio to 1.6. The highest positive likelihood ratio for a good outcome is given by the SDAI ≤3.3, at 3.0.

Recommendations dictate assessment at 3 and 6 months,[1,12] but the right time point for considering changes to therapy is less clear. At 3 months, if the patient is in remission, therapy is working and should be continued. If the patient's disease activity is unchanged, treatment must clearly be adapted. Patients not reaching the target but showing improvement at 3 months pose a greater challenge. If the patient has achieved major response criteria (SDAI 85%, EULAR good response, or ACR70), they are likely on track to achieve the selected target.[30] However, if they fail to meet minor response criteria (SDAI 50%, EULAR moderate response, ACR20), they will likely never reach the remission target at 6 months.

Once the decision has been made to adjust treatment, the question becomes which drug shall we use? Response rates to different drugs with different modes of action are remarkably similar across phases of treatment, and the decision is made more difficult by a lack of head-to-head studies.

The EXXELERATE study[31] is the first head-to-head study comparing the efficacy and safety of two TNF inhibitors in patients who are primary non-responders to the alternate therapy (Figure 2). Preliminary data (not yet published) indicate that there is no difference.

Why do compounds with different modes of action appear to produce similar response rates in patients with methotrexate failure?[32] The first explanation is the bottleneck hypothesis: that all current 'targeted therapies' interfere with a common final pathway ('bottleneck of inflammation') and therefore we deal mostly with one major responder pool.[33] The second explanation posits that responders to each of the different modes of

action do not overlap completely; some patients may respond preferentially to one treatment over another. This explanation forms the basis of precision medicine, i.e. 'delivering the right treatment at the right time, every time, to the right person'.

More patients are achieving remission and the question is then what to do if the target is reached, as stopping treatment may lead to secondary treatment failure. Approximately 34–43% of patients will be in remission at one visit, but the rate of sustained remission reduces to approximately 17–20% after a second visit.[34] Sustained remission is important, since function continues to improve over time in patients who maintain remission.[35]

The importance of detection of subclinical synovitis in evaluating initial and sustained remission is unclear. Presence of subclinical synovitis (power Doppler signal positive) is associated with an OR for radiographic progression of 12.21 ($p<0.001$).[36] Ultrasound signals are highly sensitive and sonographic findings can take years to normalise.[37]

Table 1: Remission criteria for clinical trials and clinical practice.

	For clinical practice[27]	For clinical trials[28]
Boolean criteria	SJC ≤1 TJC ≤1 PtGA (0–10 scale) ≤1	SJC ≤1 TJC ≤1 PtGA ≤1 (0–10 scale) CRP ≤1 mg/dL
Index-based criteria	CDAI ≤2.8 Where CDAI=SJC in 28 joints + TJC in 28 joints + EGA + PtGA[29]	SDAI ≤3.3 Where SDAI=SJC in 28 joints + TJC in 28 joints + EGA + PtGA + CRP (in mg/dL)[29]

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; EGA: evaluator global assessment; PtGA: patient global assessment; SDAI: Simple Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

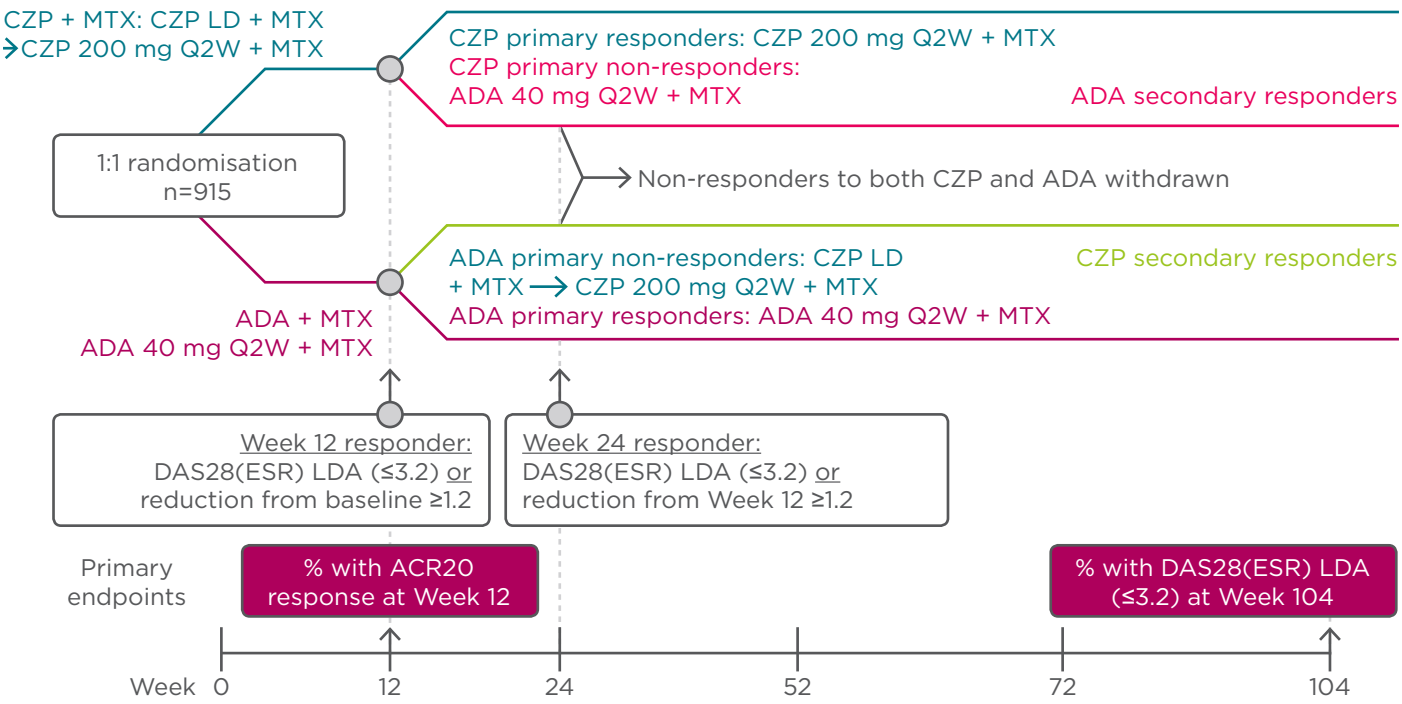

Figure 2: EXXELERATE study design.
ACR20: American College of Rheumatology 20% improvement; ADA: adalimumab; CZP: certolizumab pegol; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; LD: loading dose; LDA: low disease activity; MTX: methotrexate; Q2W: every 2 weeks.

There is currently no clinical evidence to support a change in treatment based on subclinical signs.

EULAR recommendations for tapering biologic treatment state that, if a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if treatment is combined with a csDMARD.[1] Tapering biologics (decreasing dose, or increasing intervals between doses) is better than stopping the drug. In the PRESERVE study, patients with sustained LDA on etanercept 50 mg weekly + methotrexate weekly from Weeks 12–36 were randomised to continue full dose etanercept, half dose etanercept, or placebo.[38] There was no difference between the full and half dose, but remission was much lower in the group that completely stopped etanercept. Tapering was also investigated in the C-EARLY study, where patients with sustained remission at Week 40 and 52 on certolizumab pegol 200 mg every 2 weeks + methotrexate were randomised to continue certolizumab pegol every 2 weeks, reduce dosing to every 4 weeks, or to stop certolizumab pegol.[5]

In conclusion, treat-to-target is the key concept for management of RA. In addition, a management strategy for RA needs to include guidance regarding which compound to select over another: sufficient data to support definitive recommendations are still awaited. Reaching the target of remission is only the first step, sustaining remission is the goal. In sustained remission, any drug tapering needs to be undertaken with caution, with appropriate opportunities to evaluate response built into the management plan.

Panel Discussion

Chaired by Professor Peter Taylor

Q: Is the added benefit of targeted therapies lower in DMARD-naïve (very early RA) patients?

A: There is no question that methotrexate + a biologic is superior to methotrexate alone in early RA, but methotrexate alone is also very effective. Trials describe outcomes at the group level. For an individual patient, a dramatic improvement may be seen with the switch from DMARDs to DMARDs + biologic; it is uncertain if the reverse is also true, but it could be possible for an individual patient. In the future, the hope is that we can individualise treatment better.

Q: Why escalate the dose of methotrexate instead of starting at a higher dose? Can we obviate the need for biologics by starting corticosteroids early?

A: It takes time for methotrexate to work and most guidelines recommend use of low-dose corticosteroids. The key issue for the risk-benefit profile is how much do you give at the beginning?

Patients who have control on methotrexate do not need biologics, whereas those who do not are perceived to have 'lost' 3–4 months. There is also the potential for radiologic damage, although this is likely to be minimal. While we know that combination is better than monotherapy, starting with monotherapy then stepping up to combination therapy can achieve the same clinical outcomes whilst avoiding overtreatment of patients who benefit from methotrexate alone.

Early induction with corticosteroids can provide rapid symptomatic benefit, but it is important to consider that corticosteroids have serious tolerability issues, particularly the risk of infections and serious infections. Trials are currently ongoing to assess the risks and benefits of combining methotrexate with a corticosteroid or a biologic, compared with methotrexate alone.

Q: After therapy with the first anti-TNF agent, which mechanism of action is recommended? Is it worth trying another anti-TNF agent?

A: Data from registries and observational studies suggest that a second anti-TNF agent may be as effective as any other mechanism of action.

Q: Bearing in mind differences across health economies in the threshold for access to a biologic, what are some pointers to the 'exceptional patient' who would merit early introduction of a biologic?

A: Patients with high disease activity and risk factors for rapid progression may warrant immediate treatment with a biologic. It is also important to consider the patient preference: whether they are prepared to wait for response or require rapid symptom relief. Models to evaluate the number needed to treat may also be beneficial.

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HOW PATIENT VALUE CAN INFORM CLINICAL AND RESEARCH STRATEGY

In a fast-evolving healthcare environment, with many new innovator drugs and mechanisms of action, entry of biosimilars, and increasing constraints on healthcare budgets, the patient remains the constant factor.

Current EULAR treatment guidelines highlight the need for shared treatment decisions between patient and rheumatologist.[1] With such patient empowerment comes the need for individuals to be able to fully understand the implications of their condition, as well as the rationale for, and consequences of, different management strategies. Central to the interaction between rheumatologist and his/her patient is the need to understand which element of disease and/or other factor(s) need to be 'restored' to enable a patient to reach a near normal state, which could be termed as delivering 'patient value'. Delivering patient value is critical in both drug development and patient management, and requires an appreciation of a multitude of factors, including particular patient beliefs/preferences, patient history and knowledge of the individual, the disease type/sub-type, and finally the stage and severity of symptoms.

Figure 1: Theoretical framework to help define patient value. Abstraction of obtained results, UCB Patient Value Survey, May 2015.

In an effort to advance the understanding of the relative importance of these multiple factors, a survey was conducted by UCB in 450 European Union patients with RA, axial spondyloarthritis, and psoriatic arthritis, with the majority having been treated for up to 10 years. The survey was based on a theoretical framework to evaluate patient value, exploring different dimensions of the patient experience that may be impacted by disease (Figure 1):

1. Physical symptomatic
2. Mental and emotional
3. Social
4. Economic impact (i.e. work productivity and cost of care)
5. Disease impact on family/spouse (e.g. burden on family, dependency for help, etc.)

In the section focussing on 'Understanding the Patient', the survey found that patients still suffer from active inflammatory symptoms on a daily basis, despite being treated with biologics (31%), disease-modifying anti-rheumatic drugs (41%), non-steroidal anti-inflammatory drugs (54%), or corticosteroids (24% [UCB data on file]). The impact of disease varied by region, as well as across diseases, with axial spondyloarthritis patients experiencing a higher degree of impact of their symptoms. Not surprisingly, pain featured prominently on the reported symptoms, despite all patients being treated in line with standard recommendations. Inability to perform daily tasks, joint tenderness, stiffness, and fatigue were the next most highly rated aspects. Also prominent were anxiety and depression, which were each mentioned by over a third of all patients. In terms of importance and impact on patient life, physical symptoms were followed by mental and social aspects, with mental health issues (depression and anxiety) being experienced by over a third of patients (Figure 2). Patients expressed feeling frustrated and powerless due to their condition, which could both be major factors influencing impairment of quality of life and a suboptimal patient experience. It appears that although clinicians have powerful tools in the medical armamentarium to tackle the inflammatory

burden of rheumatic disease, symptoms of pain, anxiety, and depression may often not be adequately addressed.

The question was asked: "Please indicate which 'impact on life' you consider to be 'most concerning' and which one is the 'least concerning'." Scores were indexed against the attribute receiving the highest score (pain) which was given a score of 100, e.g. less energy causes have as much concern as pain. Data shown demonstrates the percentage of the attributes chosen as most important across the survey. There was a total of 451 respondents (country bases: UK n=91, France n=90, Germany n=90, Italy n=90, and Spain n=90).

Rheumatologists (N=141) attending EULAR in Rome 2015 were asked many of the same survey questions asked to patients. While not a matched-control to the patient survey, a marked disconnect was apparent in patient-doctor perceptions of 'patient value'. There was good patient-physician consensus on the need to address and contain the physical impact of the disease; however, rheumatologists saw the emotional burden of the disease, clearly identified by patients as being in need of attention, as very low on their care priority list.

The key insight here is that patients, whilst being adequately medically treated according to today's standards, still suffer 'collateral symptoms', which could be addressed by marginally broadening the therapeutic focus. These initial findings may fuel further research into specific disease areas, as well as exploration of tailored solutions that may make a difference to patients in their quest to restore near-normality to their lives. The end goal of shared decision-making may be that, by considering these 'collateral symptoms' when treating rheumatic diseases, clinicians may impact a patients journey more via pharmacological and non-pharmacological solutions and address needs in a manner that truly, and more holistically, delivers patient value.

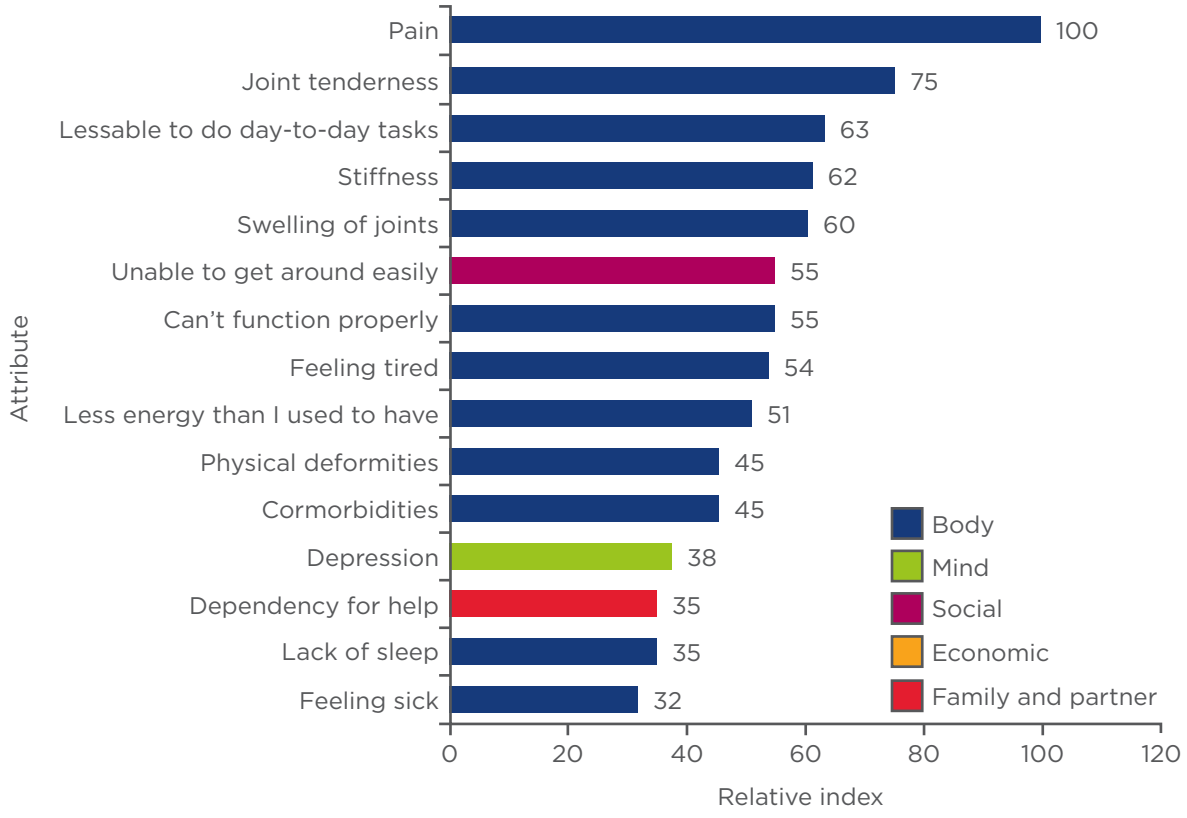

Figure 2: Top 15 relative attributes of importance to rheumatology patients. Abstraction of obtained results, UCB Patient Value Survey, May 2015.

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