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Commentary

Recommendations for an update of 2003 European regulatory requirements for registration of drugs to be used in the treatment of RA

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Abstract

Since 2003, the European Medicines Agency (EMA) document, 'Points to consider on clinical investigation of medicinal products other than NSAIDs (nonsteroidal anti-inflammatory drugs) for the treatment of rheumatoid arthritis' has provided guidance for the clinical development of both biologic and non-biologic disease-modifying antirheumatic drugs (DMARDs). In the last few years, several new products have been developed or are in development for the treatment of RA, which offer significant efficacy with regard to disease control, including prevention of structural damage and disability. Concurrently, novel insights have been gained with respect to the assessment of disease activity, joint damage and disability. New treatment strategies have been established which relate to early therapy, tight control and rapid switching of medication. Accordingly, several new EULAR/ACR recommendations have been or are being developed. Several important additions and changes are needed in the 2003 guidance to incorporate the current scientific knowledge into clinical trial design for the development of future products. Under the auspices of the Group for the Respect of Ethics and Excellence in Science (GREES), a group of experts in the field of RA and clinical trial design met to provide a consensus recommendation for an update to the 2003 EMA guidance document.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease associated with joint destruction, deformity and functional impairment. Over the past 2 decades, important progress has been made to develop and validate adequate tools to assess important clinical and structural outcomes in response to therapeutic interventions[1,2]. Concurrently, the therapeutic approach to RA changed dramatically. Key disease-modifying antirheumatic drugs (DMARDs) received European approval starting with methotrexate (MTX) in 1985 and leflunomide in 1999[3]. Then biologic DMARDs specifically targeting pro-inflammatory cytokines or immune cells, the first of these being the tumour necrosis factor alpha (TNF) inhibitors, were developed and licensed, significantly enlarging the therapeutic arena[4–7].

Notably, TNF-inhibitors in combination with non-biologic or synthetic DMARDs such as MTX, have demonstrated faster onset of action than DMARDs alone and offer better disease control including prevention of structural damage[8–11]. However, a substantial proportion of RA patients fail to respond to TNF-inhibitors plus MTX, become resistant, or develop intolerance[12–16]. To specify requirements for investigation and approval of new

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DMARDs, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) released the 'Points to consider on clinical investigation of medicinal products other than NSAIDs (nonsteroidal anti-inflammatory drugs) for the treatment of rheumatoid arthritis in 2003'[17].

Subsequently, many therapies with alternative mechanisms of action have been developed, many agents are yet in development, and several new biologics have been licensed[18–25]. Small molecules[20] may constitute yet a new generation of DMARDs. Novel insights also have been gained with respect to the assessment of and interrelationships between RA disease activity, joint damage and disability.

Nevertheless, many knowledge gaps still exist. These include understanding the biologics' relative efficacy and safety profiles compared to each other, and their optimal use alone or in combination with other therapies. To date, no clear evidence exists for a good risk/benefit profile with combination targeted biologics use [26,27]. In fact, early studies suggest no efficacy advantage but increased safety concerns[26,27]. To this effect, warnings have been added to licensed products' labels.

Current RA treatment guidelines specify that MTX, or other synthetic DMARDs, should be used first-line[28–33]. In MTX-naïve RA patients, TNF-inhibitor monotherapy has been shown to be overall clinically not more effective than MTX monotherapy, although there is significant inhibition of joint damage with TNF-inhibitor monotherapy when compared with MTX. Importantly, the efficacy of the combination of TNF-inhibitors with MTX convey better clinical and structural effects than either alone[8,9,34]. The TNF-inhibitors also have been successfully combined with other synthetic DMARDs, including sulphasalazine and leflunomide[35–37].

In clinical practice, targeted biologics are usually second-line therapy and used with a synthetic DMARD, typically MTX[31,32,38]. Supportive evidence from initial registrational trials with biologics demonstrates their advantage in a patient population which has failed or inadequately responded to MTX. A limitation of many of these clinical trials is that the new drug was tested versus placebo, both as add-on treatment to MTX[10,39–43]. The control arm therefore continued treatment with an insufficiently effective DMARD rather than being switched immediately to, or receiving concomitantly, a different drug[10,39–43].

Additional studies and new treatment strategies relating to early therapy, tight control and rapid switching of medication are being highlighted in guidelines which have been or are being developed[31,32,38,44–49] by the European League Against Rheumatism (EULAR) alone or in conjunction with the American College of Rheumatology (ACR)[32,46,50]. To this end, new ACR/EULAR criteria for the classification of RA, including early RA, also have just been developed[51,52].

Indeed, early intervention may delay or even prevent structural damage and loss of physical function, especially in comparison to DMARD treatment initiated after damage has already occurred[53–59]. Better outcomes such as tight control may also be obtained by combining synthetic DMARDs with glucocorticoids or biologics versus using more traditional approaches such as synthetic DMARD monotherapy[8,9,32,44,56,60–82]. To further optimise outcomes, when there is an insufficient response, switching to another therapy is needed[12,32,83].

To incorporate the current knowledge to optimise future regulatory requirements and approvals for new agents for the treatment of RA, a group of experts in the fields of RA, clinical trial design and/or regulatory affairs (the authors), under the auspices of the Group for the Respect of Ethics and Excellence in Science (GREES), has reviewed the current literature. They reached a consensus after a thorough discussion process utilising a physical meeting and e-mail

exchange on the following questions in order to propose a recommendation for an update of the current CHMP guidance.

- Choice of comparators and traditional indication claims
  - What is the need for placebo use and what are the limitations?
  - Should regulatory trials be conducted versus pure placebo, versus MTX plus placebo in MTX-inadequate responders, or versus active comparators, and if so, in which populations?
  - Are there specific indications for first-line therapy with biologics? In case a first-line claim is not sought, which population should be studied: DMARD non-responders, TNF-inhibitor non-responders? What are the requirements in these cases?
- Structural damage and quality of life assessments
  - What is the evidence required to demonstrate that a new biologic or DMARD slows progression of structural damage and improves quality of life?
- Potential additional claims
  - Is it conceivable to have an indication for early use, even before patients meet the RA diagnostic criteria (i.e., prevention of RA)?
  - What are the efficacy criteria acceptable for a claim of long-term remission?
- Efficacy endpoints
  - Are there alternatives to the ACR 20/50/70 response rates as primary endpoints in RA trials?

The sections below summarise the consensus on the expert group's recommendations to update the CHMP 'Points to consider' document with regard to these questions.

Choice of comparators and indication claims related to specific patient populations

Patient population

Three different RA patient populations are readily definable by their prior treatment, implying three potential indications for use of a new agent, as follows:

(1) DMARD-naïve, including MTX-naïve, patients (first-line indication),
(2) MTX- or DMARD-refractory or -intolerant patients (second-line indication), and
(3) Biologics-refractory or biologics-intolerant patients having failed one or more biologics (third-line indication).

Failure of, or intolerance to, previous treatment should be clearly prespecified, justified and documented in the protocol.

With respect to the choice of comparators, we will address the limitations and potential inappropriateness of placebo use vis-à-vis the preference for regulatory trials to be conducted in comparison with placebo below, focussing on three types of placebo control possibilities, namely pure placebo, placebo added to MTX in MTX-inadequate responders, or the use of a newly introduced active comparator with a placebo formulation of the tested drug.

In early RA or DMARD/MTX-naïve RA patients, preventing structural damage and irreversible disability with state-of-the-art therapy is important. Most contemporary randomised controlled trials of the early RA population have employed an active comparator, usually a synthetic DMARD such as MTX[8,9,60,67,70,84]. Clearly, this is the preferred trial design for this patient population.

In contrast, in established RA, new agents often are evaluated against a placebo comparator, as an add-on to a synthetic DMARD, usually MTX. Low dose oral glucocorticoids and NSAIDs are typically permitted. The current CHMP guidance document states: 'Since it would be unethical to retain a patient with active rheumatoid arthritis on placebo treatment indefinitely, the duration of placebo control must be necessarily limited. Depending on the severity and activity of the disease, 3–6 months is acceptable. For ethical reasons it is recommended to provide predefined rules for withdrawal from placebo'[17].

Eliminating or shortening exposure to placebo

The scientific advantages of a true placebo control remain the provision of an excellent assessment of the extent and onset of effect of a new agent, dose-ranging information, and a short-term evaluation of safety. However, use of a placebo control is now considered inappropriate for RA patients since tight control is instrumental in slowing disease progression and disability[44,47–49]. Also, multiple effective treatment options are available and therefore ideally placebo should be used. As mentioned, most studies of early RA and MTX-naïve populations performed recently have not used placebo but *de novo* MTX as a comparator[8,70,84–86]. Therefore, for ethical reasons, placebo exposure, as add-on therapy in the inadequate responder, should be restricted to no more than 3 months[87]. Evidence of efficacy on signs and symptoms and possibly on progression of structural damage can be obtained in this time period[87,88]. Maintenance of efficacy should be confirmed with both longer trials against an active comparator and open-label extensions[88–91].

For the longer trials, escape rules are justly required for patients who are still non-responders after their first 3 months in the study. Such escape rules usually dramatically reduce the placebo group's sample size with increasing study duration and limit between group comparability as

the balance of prognostic factors achieved at randomisation is lost. Regardless, the impact of escape rules or shortened trials may be minimal for evaluation of efficacy. Several regulatory trials of licensed targeted biologics have employed escape rules at 14–16 weeks with primary endpoint analyses at time points either before or after the escape[10,16,42,92,93], and this appears to be a feasible, though not ideal approach.

For safety, short-term placebo-controlled trials will limit the assessment of events related to longer-term exposure that could be attributable to the drug, the disease, co-morbidities, or concomitant medications. Background DMARD therapy further complicates accurate assessment of events attributable to the new compound or background DMARD therapy alone, or their combination. To allow for adequate safety evaluations, evolving study designs in RA will probably have increased dependence on large sample sizes in the phase III controlled trials and observational data from open-label extension studies[94].

Summary

To conclude this section, clinical trial data published in the recent past support that 3 months of placebo in DMARD-naïve or -intolerant patients during a phase II study is sufficient to provide robust evidence of efficacy, i.e. proof of concept, and short-term evaluation of the safety of a new compound. Means to replace placebo with other modalities, such as an active comparator, should be sought and discussed. Noting the aforementioned concepts are also applicable to phase III clinical development of new agents, the potential indications to be evaluated in phase III are described below.

Phase III studies

First-line indication: DMARD-naïve or MTX-naïve patients

In DMARD- or MTX-naïve RA patients, even those with severe active disease, MTX is still considered the gold standard[28–31,66,95–97]. A new agent could receive a first-line therapy indication either as monotherapy or in combination with MTX or other DMARDs. First-line monotherapy approval might be achieved with a direct comparison of the new agent to MTX, or alternatively, sulphasalazine, leflunomide or a combination of DMARDs, in DMARD- or MTX-naïve patients[98]. As a different onset in efficacy between test and active comparator may have an impact on the results, the choice of active comparator should be appropriate and substantiated. The new agent would need to demonstrate statistically significant efficacy which is at least non-inferior to that of MTX in terms of signs and symptoms, structural damage and physical function with a similar safety profile[99]. For assessment of safety, monotherapy data are needed against an active comparator with a well known safety profile to allow for a more accurate assessment of adverse events attributable to the new compound.

To receive an indication as first-line combination therapy, a comparison of the new agent alone, MTX alone, and the combination in the same trial would probably be required (this trial design would permit assessment of monotherapy also). At least non-inferiority and more likely, superior efficacy with the combination therapy versus the comparators would have to be expected. The combination therapy would require extensive safety comparisons to the comparator group.

Second-line indication: MTX-refractory or intolerant patients

Methotrexate-refractory patients with RA should have demonstrated inadequate clinical response to previous MTX therapy of at least 4 months' duration, with a dose between 20 and 25 mg for at least 2 months, unless intolerant[28]. Studies with a new investigational product could be designed against placebo, with both arms continuing MTX, for the initial 3 months. In this scenario, the new agent would need to demonstrate superior efficacy to placebo regarding signs and symptoms and ideally also structural damage or physical function at 3 months. After 3 months, the comparator arm could be switched to, or receive as add-on, another drug licensed for the treatment of RA, e.g., a synthetic DMARD such as leflunomide or sulphasalazine or a biologic such as a TNF-inhibitor, in order to continue evaluation of the new agent's comparative safety and maintenance of efficacy long-term.

A limitation of the add-on to MTX design is that data regarding overall absolute treatment differences between the biologic agents themselves are not obtained. As long as direct comparisons with a TNF-inhibitor or other biologic DMARDs are not performed, it remains difficult to quantify if there is a preferential advantage for use of any biologic over another.

Third-line: Biologics-refractory or intolerant patients

Biologics-refractory RA patients should have demonstrated inadequate clinical response to previous TNF-inhibitor/synthetic DMARD combination therapy of at least 3 months' duration before entering the study. Studies could be designed against a background DMARD such as MTX plus placebo (for 3 months) or the prior biologic therapy, unchanged upon enrolment into the study. The new agent would need to demonstrate superior efficacy to placebo regarding signs and symptoms and ideally also structural

damage or physical function at 3 months. After 3 months, to demonstrate maintenance of benefit with the new agent, comparators could be other licensed biologics or synthetic DMARDs which the patients had not previously received.

Comparative trials among biologicals

An additional question is: *For approval of a biologic agent, are comparative trials versus other biologicals a requirement?*

Although not formally recommended, as multiple effective therapies are available to RA patients, a phase III study comparing the new agent plus or minus a synthetic DMARD to a TNF-inhibitor plus synthetic DMARD is highly advised. The TNF-inhibitors with MTX are considered the best comparators as they show the tightest confidence intervals for efficacy, have the longest safety record of the targeted biologics, and comprise multiple established licensed agents with similar efficacy and safety findings. The ideal population is the MTX-failure/inadequate responder population with moderate-to-severe RA, for which a TNF-inhibitor plus MTX is the current standard of care. A true head-to-head study against a TNF-inhibitor/MTX combination would require a comparison to the new agent both as monotherapy and in combination with MTX. Efficacy comparisons would need to be made on signs and symptoms, physical function, and structural damage. At least non-inferior efficacy against the TNF-inhibitor/MTX combination would need to be demonstrated in at least signs and symptoms and ideally also physical function and structural damage, accompanied by a similar or better safety profile. If inferiority in a secondary endpoint is observed for the new agent plus or minus MTX versus the TNF-inhibitor/MTX combination, there should be an impact on the new agent's Summary of Product Characteristics (SPC).

Designing such comparative studies may prove to be challenging. Observed differences between a new agent and a TNF-inhibitor are likely to be small, which may make results difficult to interpret. Furthermore, the potential need for a very large sample size to demonstrate non-inferiority is a recognised obstacle to study conduct.

Structural damage, physical function and quality of life assessments

Duration of trials on joint damage

For a structural damage indication, the 2003 CHMP 'Points to consider' document specifies, 'In order to demonstrate efficacy in radiological terms using technology currently generally available, an observation period of no less than 1 year is required. The observation period needed is not less than 2 years, showing sustained effect for the effect after the first year. A shorter duration of study has to be adequately justified and efficacy within a shorter time frame has to be documented unequivocally.'

Subsequently, data from multiple targeted biologics have shown that radiographic benefits detected as early as 6 months are maintained at both 1 and 2 years with supportive findings in physical function[8–10,34,42,100]. Further data support the conclusion that current technology has sufficient precision to detect a difference in structural damage progression at the study group level at 3–6 months[88].

Therefore, to obtain a structural damage claim, randomised, double-blind studies should be conducted against an appropriate comparator for the initial 3 months. At the study's 3-month time point, to minimise patient exposure to inadequate therapy, the requirement to confirm short-term structural damage changes with longer-term follow-up could be addressed by instituting one of the following options:

- Implementation of escape rules to provide rescue therapy for non-responders; others could continue therapy unchanged.
- Initiation of open-label therapy with the new agent by all patients. Open-label assessment of X-rays is not an issue as the readers of the X-rays are blinded to treatment and sequence.
- Re-randomisation of the comparator group patients to either another standard active treatment (e.g., a licensed biologic or synthetic DMARD) or the new agent.

In each scenario, all patients would receive X-rays of hands and feet at 3 months/time of escape and at different time points up to 12 months for comparative purposes.

Imputation of radiographic data

Imputation of missing and 3-month data to results at 6–12 months, although necessary, remains methodologically problematic – radiographic data are highly skewed as many patients, even with active disease, do not progress within 1 year[101]. However, with the first design, any early difference (i.e., more rapid progression in the placebo group) is likely to be retained at later time points since rescue is limited to the worst patients. With the latter two designs, all patients receive active treatment after 3 months, so should show a subsequent slowing of the rate of progression which for the former comparator group should approach that of the original active treatment group. For the original active treatment group, maintenance of the effect seen at 3 months can be documented by within group comparisons with the results seen at 6 and 12 months. Failure to show a structural benefit at 3 months, as possibly seen with agents with slower onset of effect should not preclude a structural damage indication if such efficacy is clearly shown at subsequent time points.

Currently, licensed targeted biologics with a structural damage indication have also demonstrated benefits in signs and symptoms and/or physical function. It may be difficult for a new agent to obtain an indication for structural damage alone, unless it conveys added benefit combined with another agent that impacts signs and symptoms and physical function.

Physical function and quality of life

For physical function, the Health Assessment Questionnaire (HAQ) is recommended as it has shown reliability and sensitivity to change and has been validated over time[102–104]. In clinical trials, improvement in functional disability should be correlated with disease activity reduction and prevention of structural damage[55,105,106]. Changes demonstrated at 3 months should be maintained or improved through the first year. As a caveat, the HAQ score reflects both a reversible component related to disease activity and an increasingly irreversible component related to joint damage progression[54,55,104,107]. With respect to quality-of-life assessment, several well validated instruments are available, some of which are mentioned in Tables 1A and 1B.

Potential additional claims

Claim for treatment of early RA and remission

The EULAR recommends 'Patients at risk of developing persistent or erosive arthritis should be started with DMARDs as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatic diseases'[46]. Recently published studies do suggest that DMARD treatment of early undifferentiated arthritis could prevent the development of RA according to 1987 classification criteria[67,108,109]. Identification of the right populations which will progress to RA and therefore need respective therapy is crucial. Predictors include the presence of high swollen joint counts, elevated C-reactive protein (CRP) levels, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA)[110–112]. The EULAR and ACR have developed new RA classification criteria in 2010[52,64]. New trials should employ these new criteria, but at the same time also report on the results obtained when using the subpopulation fulfilling the old criteria, for reasons of comparability with previous studies.

Similarly, the EULAR and ACR have developed new criteria for RA disease remission[113], since clinical remission defined by a DAS28 < 2.6 does not exclude a significant level of residual disease activity[49,114–118]. These new

Table 1A. Suggested time points for efficacy assessments in moderate to severe rheumatoid arthritis.

Specific claim	Current CHMP guidance Time points (months)		GREES suggestion Time points (months)	
	Controlled	Open label*	Controlled	Open label*
Disease activity (signs and symptoms)	3–6	n.a.†	3	Additional 0–3†
Joint damage	12	Additional 12	3	Additional 9‡
Physical function	12	Additional 12	3	Additional 9

*Subsequent to the controlled phase.
†Usually, more profound response rates (such as ACR50 and ACR70 or remission) peak later than the 3-month time point. For safety assessments, an additional open-label assessment period in combination with the controlled period of study would be required to provide for a total of at least 12 months of evaluation.
‡Includes assessment at the 3-month time point, i.e., 6 months from baseline.
n.a., not applicable.

Table 1B. Suggested efficacy assessments in moderate to severe rheumatoid arthritis.

Claim	Instruments	
	Current CHMP guidance	GREES suggestion
Disease activity (signs and symptoms)	ACR response; Paulus; DAS/DAS28 including EULAR response	ACR response; DAS/DAS28 including EULAR response; SDAI, CDAI; ACR-EULAR remission definition
Joint damage	Sharp score including modifications; Larsen score	Sharp score including modifications; Larsen score
Physical function	HAQ, AIMS (function and quality of life), SF-36 (PCS, PF)	HAQ, AIMS (function and quality of life), SF-36 (PCS, PF)

ACR, American College of Rheumatology; AIMS, Arthritis Impact Measurement Scale; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; DAS28, Disease Activity Score-28 joint count; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; PCS, Physical Component Summary; PF, Physical Function domain; SDAI, Simplified Disease Activity Index; SF-36, Short-Form 36-item Health Survey.

criteria have been recently published and comprise a Boolean definition with four core set variables (tender joint count, swollen joint count and patient global assessment all ≤1 on a 28-joint count or a 1–10 scale, respectively, plus CRP ≤ 1 mg/dl) and an index-based definition (SDAI ≤ 3.3); it is recommended that one of these should be selected as an endpoint and both be reported in each trial. In addition a preliminary definition for clinical practice that does not contain CRP, i.e. a Boolean definition with the three mentioned core set variables and CDAI ≤ 2.8, was also recommended[119,120]. Remission is an increasingly important outcome in clinical trials. However, while lack of clarity regarding required study duration, choice of comparator and efficacy endpoints preclude designing clinical trials at this time that could support a claim either for the treatment of early RA or disease remission, given the new ACR-EULAR definition such trials may be more easily designed in the future.

Claim for prevention of morbidity and mortality due to RA

A claim for the prevention of cardiovascular morbidity and/or mortality may be possible, as RA patients have an increased risk of cardiovascular disease not always related to the presence of traditional risk factors[121]. Assessment of the effect of novel therapies on cardiovascular outcomes, such as the reduction of cardiovascular risk, would have to be appropriately designed and require large sample size and long-term follow-up, unless short-term surrogate markers can be identified and validated. Use of hazard ratio estimates is recommended but adjudication of cardiovascular secondary endpoints would also be required. The impact of specific medications (e.g., glucocorticoids, statins, NSAIDs/coxibs) should be evaluated via subgroup analyses.

Similarly other possible claims related to pertinent safety outcomes such as infections, malignancy rates, or overall mortality could be considered after completion of appropriate clinical trials.

Endpoints

Are there alternatives to ACR 20/50/70 as primary endpoints in RA trials?

Generally only validated composite endpoints are acceptable as primary endpoints to document efficacy in signs and symptoms[122] for regulatory purposes. These include the Disease Activity Score (DAS) (including EULAR categories)[123–126] and ACR response criteria[127–129] both widely accepted and used in clinical trials. Two newer validated composite endpoints which also perform well are the Simplified Disease Activity Index (SDAI)[1,2,130,131] and Clinical Disease Activity Index (CDAI)[132,133].

The ACR 20/50/70 response[127,128] is a dichotomous outcome designed to assess at least 20/50/70% improvements in tender and swollen joint counts and in at least three of the following five measurements: an acute phase reactant, i.e. CRP or erythrocyte sedimentation rate (ESR), the Physician's and Patient's Global Assessments of Disease Activity, the Patient's Assessment of Arthritis Pain, and the HAQ. The ACR20 response has been shown to discriminate well between active therapy and placebo[127,128] and, therefore, is a usually preferred primary endpoint for initial phase III trials.

In contrast to the ACR response, the DAS, SDAI, and CDAI all combine single measures into an overall continuous measure of RA disease activity. The DAS components include the 28 tender and swollen joint counts (DAS28), ESR or CRP, and the patient's general health assessment[123–126]. The SDAI is a numerical sum of the 28 swollen and tender joint counts, Patient's and Physician's Global Assessments of Disease Activity and CRP; the CDAI uses the same approach but without CRP[1,131].

Although the DAS, SDAI and CDAI, unlike the ACR response, do not include a physical function assessment in their core components[134,135], the ACR response criteria assessment is not always impacted by the HAQ component[53,54,105,129,136,137]. Furthermore, all four composite indices correlate with changes in disability and progression of joint damage and therapeutic efficacy demonstrated at 12 weeks with these tools appears predictive of more robust long-term benefit[90]. This indicates physical function is not an absolute requirement in a composite score.

Recently, the ACR/EULAR have recommended that data from RA clinical trials should report (1) the level of disease improvement, and (2) the state attained at study endpoint[50]. The ACR response criteria assess the former, not the latter. The DAS (including the EULAR response criteria), SDAI, and CDAI assess both. All four are among the variables recommended by the ACR/EULAR for reporting in clinical trials[50]. The response criteria's core component data must also be reported and all such analyses must be pre-specified[50].

Personalised therapy

As understanding of RA pathophysiology and therapeutics advances, tailoring therapy to the individual patient becomes more of a reality. Beyond traditional biomarkers such as ESR, CRP, RF, and ACPA, as well as genetic markers such as specific HLA subtypes, the tools do not yet exist to provide personalised medicine in RA, or tailor therapeutic trials. Eventually, data on off-target effects and genetics, once validated, may serve to guide clinical development[138–144]. Currently, such data are considered supportive of clinical findings but not direct endpoints in and of themselves. A guidance document on these new aspects will be needed in the near future.

Summary and recommendations

Summary

The last decade has brought significant advances in the therapeutics of RA. As a result of the increased knowledge base, the authors recommend that the 2003 CHMP Guidance be revised as summarised in Tables 1A and 1B. These suggestions include recommendations with clearer delineation of pathways to achieving first-, second-, and third-line indications for the treatment of RA with shorter timelines for development.

Conclusion

Significant advances have been made in understanding and assessing the RA disease state, its outcomes, and the impact of new therapeutics in the past 2 decades. The European regulatory guidance for rheumatoid arthritis disease-modifying agents needs to incorporate current scientific knowledge to optimise future regulatory requirements and approvals for new agents for the treatment of RA. A group of RA experts has provided a consensus opinion on pathways for new therapeutics to achieve first-, second-, and third-line indications for the treatment of RA with shorter timelines for development

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