Lessons from negative phase 3 trials in rheumatoid arthritis anno 2023

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A recent phase 3 trial (contRAst 3) with otilimab, a drug targeting granulocyte-macrophage colony-stimulating factor (GM-CSF), was reported by Taylor *et al* to be negative in a population of patients with rheumatoid arthritis (RA) refractory to conventional synthetic(cs)DMARDs and advanced therapies, including biological(b) DMARDs and targeted synthetic(ts) DMARDs.[1] The trial not only failed to meet its primary endpoint with a weekly subcutaneous (SC) dose of 150 mg otilimab compared with placebo on top of csDMARDs, but also did not demonstrate non-inferiority to the active comparator sarilumab. Two other phase 3 trials comparing otilimab with placebo or tofacitinib in patients with an inadequate response to csDMARDs or bDMARDs (contRAst 1 and contRAst 2) showed statistical benefit over placebo but less than tofacitinib.[2] Otilimab was the first drug with this mode of action (MOA) making it to phase 3, based on promising preclinical data confirming the rationale of targeting GM-CSF in RA and on phase 2 trial results.[3 4] Another promising compound targeting GM-CSF, mavrilimumab was not pursued to phase 3, after a phase 2 trial with 100 mg SC every other week versus golimumab 50 mg SC every 4 weeks on top of methotrexate (MTX).[5] The study programme with namilumab was not pursued either, after a small dose finding study on top of MTX in patients refractory to csDMARDs or with an insufficient response or intolerance for anti-TNF therapy.[6]

The early biological era was a period of euphoria with the approval of several new drugs with different MOA. With the introduction of JAK inhibitors (JAKi), competent authorities have become more restrictive and demanding.[7] Drugs with a new MOA will inevitably enter the market less frequently in the coming years, given the important financial implications of trial programmes and the difficulty of providing evidence for improved efficacy and safety compared with available competitors. Making use of existing drugs more effectively could be an alternative as demonstrated with SC infliximab administration improving pharmacokinetics versus intravenous infliximab.[8] There is also a need for strategy trials, preferably starting with optimisation of the initial therapeutic approach but also investigating, within a T2T approach, the ideal sequence of drugs depending on their MOA, taking into account potential individual clinical and molecular signatures.

We provide a critical analysis on the contRAst studies, trying to draw lessons for future clinical trials and daily care: how should we proceed in solving the remaining unmet need of patients with RA?

(1) Was there enough evidence in phase 2 otilimab trials to proceed to phase 3?

- An interesting meta-analysis by Kerschbaumer *et al*[9] concluded that phase 2 trial results systematically seem to overestimate phase 3 results in RA. Drivers of this overestimation were, for instance, the higher number of minimally required swollen and tender joints at inclusion in phase 2 trials. Trials using the 28-joint count were also associated with an increase in phase 2/3 efficacy differences. Therefore, the methodology of the main phase 2 otilimab trial[4] was probably not ideal. Using DAS28 remission as the primary outcome was already criticised by Bykerk in an accompanying editorial.[10]
- In the phase 2 dose finding trial, otilimab was injected weekly for 5 weeks and thereafter 2 weekly. A switch to the highest dose of 180 mg was allowed at week 12 in patients not achieving a predefined efficacy level. The dosing regimen and PK levels could potentially be an explanation for the suboptimal phase 2 results. Bykerk discussed this in her editorial and assumed that 150 mg weekly at least would be needed given the high antibody clearance and low bioavailability. Thus, the phase 2 trial left uncertainty for optimal phase 3 dosing. However, despite confirmation of the biological effect of 150 mg otilimab SC as reflected by a decrease in CCL17 levels, the phase 3 trial did not show superiority to placebo.
- In the phase 2 trial 60% of patients took glucocorticoids (GC) which might have influenced results. While GC use was similar across treatment arms this will have had impact on baseline data and the ability to improve during study. It is unlikely that the influence of GC use in placebo controlled trials as documented for X-ray damage[11] would be limited to this outcome only.
- It seems that an important reason for continuing to phase 3 was the assumed additional benefit of otilimab on pain. Indeed, post hoc analysis of the phase 2 trial[4] revealed that otilimab was associated with a higher proportion of patients with a ≥10 mm difference on a 100 mm visual analogue scale (VAS) (minimal clinically important difference (MCID)) versus placebo and the largest difference was in the 180 mg dose group. This patient-reported outcome gets much attention nowadays as an important unmet need in current RA treatment. While pain control is indeed a preferred goal by patients, we doubt that the preclinical data about the role of GM-CSF in pain[12] and the otilimab phase 2 results were sufficient to predict a superior effect on this parameter. The phase 3 results with otilimab seem to confirm this. In our own early RA research, we showed that rapid and persistent disease control and not treatment type was associated with favourable patient-reported health (including pain) and illness perceptions at year 1, but baseline psychosocial variables mattered most.[13] The latter deserve more study on top of evaluating drug efficacy in this field.

(2) Are there possible flaws in the contRAst 3 phase 3 design?

- ContRAst 3 was part of a phase 3 programme in a population of RA patients considered refractory to current treatments, in this study ≥1 bDMARDs or tsDMARDs with or without csDMARDs. More than 80% of patients received MTX at baseline and 'were permitted to continue this' while GCs were taken by up to 50% of study participants and the baseline dose needed to stay unchanged 'except for side effects'. This was a blinded randomised placebo-controlled trial and after evaluation of the primary endpoint at 12 weeks escape to active

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treatment was possible for ethical reasons. For this phase 3 otilimab trial, the IL6 receptor-antagonist sarilumab was chosen as comparator drug because in the current era most refractory RA patients would have been previously exposed to a TNF blocker. Primary endpoint was the ACR20 response with otilimab compared with placebo. CDAI was evaluated among other secondary endpoints to overcome the CRP bonus of an IL6 antagonist. Some reflections are needed:

- The otilimab dosing schedule chosen for this phase 3 trial was already commented above. Also given the inferior results of the 90 mg weekly dose in phases 2 and 3, one wonders if 150 and 180 mg weekly would not have been a better choice for phase 3, also because no major safety issues were recorded in this and previous trials.
- The high placebo response of about 38% even for an ACR20 at week 12 in contRAst 3 is stunning as the population studied is supposed to be very refractory. Placebo responses are different in different parts of the world where also this trial had to recruit and this has already been reported earlier in the biological era[14] as part of the explanation for negative trials. Of course, this is a randomised study but differences in reporting, in expectations, in social and cultural environment might result in different perceptions about treatment effect and different treatment adherence. As detailed in suppl. fig 4 of this phase 3 report, there is certainly in Asia a relatively high placebo response and although study participation is low in this region it cannot be excluded that these factors could have influenced results.
- Also detailed MTX intake during the study is not reported and as in many other trials GC intake during the study is unclear. Problematic perceptions on MTX could lead to poor compliance and we would call for this aspect to be given more attention in future studies. The phrasing in contRAst 3 regarding background csDMARDs as 'were permitted to continue this' therefore seems strange. A study by Kerschbaumer *et al* clearly demonstrated the possible impact of pre-existing background therapy in placebo-controlled trials[15]: patients continuing a previously insufficient MTX treatment show higher clinical responses on placebo likely because of more consequent intake of the background therapy during trial. One might argue that here the baseline dose was sufficient but correct intake of background treatment before and after inclusion is a point to consider.
- The important role of expectations and perceptions is also demonstrated by a sudden improvement of efficacy after week 12 in contRAst 3, probably because patients knew they would receive active treatment from that point onwards. This trial was comparing efficacy of otilimab with placebo but also with an active comparator. The influence of this on patients' perceptions and expectations is difficult to predict. While in general placebo-controlled trials lead to smaller effect sizes of the study drug compared with the same compound in head-to-head trials,[16] the effect of a mix of a placebo and an active comparator in the same trial is more difficult to judge in this regard. Overall, the problem of a high placebo response in clinical trials is increasing during the last two decades as discussed by Bechman *et al*.[17] These authors conclude that evolution of the phenotype of RA patients available for trials, changes in trial design and expectation bias are possible explanations. These issues should get more attention especially when evaluating novel agents against established therapies. More precise selection of patients (eg, definition of refractory disease), optimal background treatment, monitoring of csDMARD compliance and outcome measures which are less vulnerable to placebo response will be needed in future active comparator trials.

(3) What is the current unmet need for patients and how does this has to impact future studies?

- The increasing availability of drugs with different modes of action is judged important by the European Alliance of Associations for Rheumatology[18] and added as an overarching principle since the 2019 update of the recommendations for the management of RA. Advances in drug treatment have clearly improved well-being of our RA patients. Classical drug trials are, however, not informing us fully on how to further improve care for individual patients, a paradox that was already discussed in 2007 in an editorial by O'Dell.[19] There is meanwhile already a shift towards trials with an active comparator design as suggested by O'Dell, but the GM-CSF phase 3 programme discussed here illustrates that the objectives of such trials are hard to reach. Importantly, this also comes with a risk of misunderstanding or disregarding the potential value of a new compound for specific subgroups of patients with remaining unmet needs that currently lead to high societal costs due to unsuccessful drug cycling.
- Contemporary RA papers all too often report that '30%–40% of patients are currently not responding adequately on available drugs'. This might apply to the result of individual classical RCTs, but strategy trials such as BeSt[20] and CareRA[21] incorporating T2T in a well-defined patient population illustrate that we can do much better. From our point of view the ideal candidate for advanced therapy both in clinical practice as in clinical trials would be a patient not responding sufficiently to such an intensive initial strategy.[22] Today, unfortunately, the treatment history of patients included in clinical trials can be very heterogeneous, with some having previously received delayed or inappropriate treatment. This has an important effect on placebo responses and a priori responsiveness to any kind of new drug.
- ContRAst 3 also shows that it is difficult to find the correct patients for inclusion as demonstrated by the important number of participating sites, some with very low inclusion numbers. In many centres the average disease activity level of patients with RA is below the threshold for study participation. Also, some patients have remaining complaints despite decreased inflammation. A definition of refractory disease just by number and type of failed DMARDs is not working, as was nicely reviewed by Melville *et al*.[23] Risk factors for refractory disease include treatment delay, therapeutic strategy, baseline disease activity and function, female gender, smoking, obesity and lower socioeconomic status. Coexisting non-inflammatory pathology might also lead to overinterpretation of disease activity, in turn influencing responses to novel DMARDs in trials. Increasing treatment options in recent years have resulted in more rapid b/tsDMARD cycling and patients ending up earlier in a so-called 'refractory' status. Compliance with treatment recommendations, early diagnosis and treat-to-target using validated outcome measures, addressing modifiable risk

factors and comorbidities, in other words good rheumatology practice, could probably have prevented a refractory status in many of these patients. In a recent early RA JAKi trial in csDMARD naïve patients, for example, about one-third of the participants were left on GC monotherapy for more than 1 year before inclusion.[24] We can and should do much better than this!

We can conclude that new drug development in RA will become more challenging in the near future but not impossible. Phases 2 and 3 trial designs will need more stringent selection of participants, clever patient stratification and more relevant outcome measures. Critical reflections about what exactly is a refractory disease status are necessary and ultimately every effort has to go to quality improvement of daily rheumatology practice following existing recommendations. This will restrict the number of patients with unmet needs using the existing therapeutic arsenal and appropriate non-pharmacological care, before selecting them for therapy trials with novel compounds. Mastering all this in the world of trials will be demanding and perhaps also more costly but without this there can be no progress. Negative trials are disappointing given the lack of a direct return of investment but can sometimes also be excellent food for thought, in view of avoiding future negative and non-contributing trials, which are even more costly.

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