

# Novel targeted therapies: the future of rheumatoid arthritis? Mavrilimumab and tabalumab as examples

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Rheumatoid arthritis (RA) control and outcome has greatly improved with the efficacy of biologic disease-modifying antirheumatic drugs (DMARDs)<sup>1</sup> combined with early effective management and treatment targeting remission or low disease activity.<sup>2-3</sup>

However, although biologic therapy-blocking key molecules involved in the pathogenesis of RA has greatly improved RA management, some needs are still unmet. About 30% of patients with RA show inadequate response to the first biologic therapy,<sup>4-8</sup> which is usually a tumour necrosis factor (TNF) blocker, currently considered with methotrexate (MTX) as the 'gold standard' in RA therapy.<sup>1</sup> After failure of at least one TNF inhibitor, the response rate of biological agents is 20–40% after adjustment for the placebo response.<sup>9</sup> In addition, the response may decrease over time in some patients. Finally, only a few patients achieve remission or low disease activity, the rate being lower for established than early RA.<sup>2</sup>

Since the remarkable but partial success of TNF inhibitors, tremendous efforts have been made to offer additional treatment options for RA patients. Thus, several biologics drugs with other modes of action have been developed, which block cytokines other than TNF or cells involved in the pathogenesis of RA.<sup>10</sup> This has led to the licensing of biological DMARDs inhibiting interleukin 1 (IL-1) (anakinra), IL-6 receptor (tocilizumab), B cells (rituximab) and T-cell costimulation (abatacept).<sup>1-3</sup> The availability of this variety of biological drugs has offered additional strategies for rheumatologists

in daily practice, but refractory patients remain, and many still have active disease and progressive disability. Another 'fashionable' and more recent strategy has been to try to identify biomarkers that could identify subpopulations of patients with better response to a specific drug.<sup>11</sup> However, biomarkers, so far, have failed to predict the clinical response to any biological or synthetic DMARD at the individual patient level, and personalised medicine, while undoubtedly of great potential and tremendous research and practical interest, still remains a long-term prospect in RA management.<sup>12</sup>

In this issue of *Annals of the Rheumatic Diseases*, Burmester *et al*<sup>13</sup> and Genovese *et al*<sup>14-15</sup> report on phase II clinical trials of two new biological agents with novel mechanisms of action. These new biologic DMARDs target granulocyte-macrophage colony stimulating factor (GM-CSF) receptor  $\alpha$  and B-cell activating factor (BAFF), molecules that may play a role in the pathogenesis of RA.<sup>10</sup>

Mavrilimumab, a human monoclonal antibody anti-GM-CSF receptor  $\alpha$ , is a competitive antagonist of GM-CSF signalling. While GM-CSF is known to most of us as a growth factor for leukocytes (and used therapeutically as an alternative to G-CSF for the treatment of neutropenia), it also modulates functions of myeloid cells such as macrophages.<sup>16</sup> Therefore, blockade of GM-CSF could be expected to result in a decrease of leukocyte activation and attenuation of autoimmune inflammation. In a previous report, Burmester *et al*<sup>17</sup> evaluated the safety, efficacy and pharmacokinetic and pharmacodynamic profiles of a single infusion of mavrilimumab in a double-blind, placebo-controlled, dose-escalating study of patients with RA who concomitantly received MTX. This preliminary study suggested encouraging effects of mavrilimumab for RA. In the current study, Burmester *et al*<sup>13</sup> evaluated the 12-week safety and efficacy of subcutaneous mavrilimumab (10, 30, 50 or 100 mg

every other week) versus placebo in patients with RA (n=239) with inadequate response to MTX. All patients received background MTX. Treatment with mavrilimumab met the primary endpoint (reduction of DAS28 c-reactive protein (CRP)  $\geq 1.2$ ) as compared with placebo at week 12. This positive result was mainly driven by the higher dose (100 mg), with clinical effect observed within the first 2 weeks of treatment. At 12 weeks, clinical improvement as measured by American College of Rheumatology (ACR) response rate, was greater for patients (n=39) who received 100 mg mavrilimumab every other week than placebo. ACR20, 50 and 70 response rates were 69.2, 30.8 and 17.9% versus 40.0, 12.0 and 4.0%, respectively, for patients receiving placebo (intent to treat (ITT) population with non-responder imputation (NRI)). Low disease activity (defined as DAS28 CRP score  $\leq 3.2$ ) did not significantly differ between active treatment (30.8% with 100 mg mavrilimumab) and placebo (20.0%). CRP level and erythrocyte sedimentation rate differed significantly for mavrilimumab versus placebo. No particular safety signal was noted and, specifically, anti-GM-CSF treatment did not appear to lead to clinically significant leukopenia.

Tabalumab is a human anti-BAFF monoclonal antibody that neutralises both membrane-bound and soluble BAFF (also known as B Lymphocyte Stimulator (BLyS), as TNF- and APOL-related leukocyte expressed ligand (TALL-1) and as CD257). BAFF is a cytokine of the TNF family required for B-cell survival.<sup>18</sup> Although the precise role of B cells in the pathogenesis of RA remains unclear, the established efficacy of rituximab strongly supports the idea that downregulation of (autoreactive) B cells may benefit patients with RA. Genovese *et al*<sup>14</sup> report the results from a 24-week double-blind, placebo-controlled, dose-ranging trial of 158 patients with active RA receiving MTX. Tabalumab (1–120 mg) or placebo was given subcutaneously every 4 weeks. Tabalumab met the primary endpoint—dose-response relationship based on a statistical model of the proportion of patients achieving ACR50 at week 24—as compared with placebo. At week 12, observed ACR20 and 50 response rates were significantly higher with only the 120 mg tabalumab dose as compared with placebo (66.7% and 33.3% vs 33.3% and 11.1%, respectively (ITT with NRI)). At week 24, only the ACR50 response

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rate significantly differed between the 120 mg dose and placebo. The response with any other dose did not differ from that with placebo at any time. The change in CRP levels was similar among treatments. The incidence of infections was greater with tabalumab than placebo, with no dose-related effect. No other safety signal was observed. Genovese *et al*<sup>15</sup> also reported efficacy and safety of tabalumab in patients with RA with inadequate response to TNF blockers. Patients (n=100) were randomised to receive, with background MTX, placebo or two intravenous doses of tabalumab (30 or 80 mg) at weeks 0, 3 and 6. The primary endpoint was not met: the authors found no significant difference in ACR50 response between tabalumab treatment (12.7%) and placebo (2.9%) at week 16. Likewise, ACR20 response rates did not differ between groups: placebo 17.1%, tabalumab (30 mg) 25.7%, tabalumab (80 mg) 28.6%. Some secondary endpoints such as DAS28-CRP changes did differ. Based on these phase II trials, a phase III trial programme was initiated, but in February 2013, Eli Lilly, the manufacturer of tabalumab announced that it will discontinue the Phase III RA programme for tabalumab due to lack of efficacy in interim analysis. The decision was not based on safety concerns, and the tabalumab Phase III programme for systemic lupus erythematosus is still ongoing and will continue as planned.<sup>19</sup> These data are in line with previous trials with two other biologic therapies (belimumab, ataccept) that target BAFF, which both showed disappointing clinical responses in patients with RA.<sup>20 21</sup>

The findings from the three trials reported in this issue, as well as some previously published trials, provided initial support for the hypothesis that these two new biological therapies could offer some clinical efficacy compared with placebo, at least in patients with RA with suboptimal response to MTX. However, the magnitudes of the therapeutic responses in these trials were modest, and their clinical relevance was, therefore, not entirely clear. In the case of tabalumab, the phase III trial led to the conclusion that the efficacy was not sufficient to warrant further development. For mavrilimumab the question is still open, and we do recognise that those trials were only phase II, and that the somewhat weak efficacy results may be related to drug dose or methodological issues, including study design, primary endpoints and sample size calculations.

Regardless, the ACR20 and 50 response rates seem modest as compared with those obtained in the phase II trial of the most recent drug approved for RA,<sup>22</sup> and are in the lower range of the response rates reported for the therapy of currently marketed biologics when added to MTX.<sup>23 24</sup> In addition, a truly effective therapy for RA would be unlikely to miss endpoints such as acute-phase reactant changes. While for the sake of our patients we hope that anti-GMCSF will prove to be 'successful', the results to date only allow more guarded optimism. One does hope that both these novel biologics might find a role as outstanding treatments for certain well defined patient groups within the entire field of rheumatology.

For those who develop antirheumatic drugs, a key question is what level of response in phase II would be sufficient to proceed to phase III: as it turned out in the case of tabalumab, a more pessimistic reading of the phase II results could have avoided the huge expenses involved in the phase III programme and spared the participating patients the 'double-whammy' of being treated with an ineffective drug while being exposed to potential risks. Unfortunately, the determination when to proceed from phase II to phase III is enormously difficult to make, and some currently available drugs had modest phase II results. Perhaps the most prudent advice would be to follow through on ambiguous phase II results with an additional phase II trial rather than a full-fledged phase III programme.

In a wider perspective, we may have to reconsider our expectations when viewing the development of therapies with novel mechanisms of action for patients with RA. Because of the variety of therapies available for RA, new targeted compounds without clear benefit, compared with existing drugs are unlikely to improve management of RA. Ideally, these new drugs should provide a better benefit:risk ratio for the whole RA population as compared with existing therapies, such as TNF blockers and MTX, or at least provide a clear advantage in a subset of patients such as those with inadequate response to anti-TNF agents. All biological drugs currently available show similar response rates and same frequency of good outcome regardless of their mechanisms of action, with respect to the RA population where they are evaluated (early RA, inadequate response to MTX or TNF).<sup>9 12 23</sup> In addition, attempts to

combine two targeted biologic agents have failed to show additional efficacy, while at least two such combinations have demonstrated significantly increased toxicity.<sup>25 26</sup> These data do not suggest that focusing on the difference in mode of action will improve the therapeutic success for RA.

One of the major unmet needs in RA is the group of patients for whom anti-TNF agents have failed. We could also add the patients with secondary loss of response and the 'partial responders' who still have some active disease despite improvement with first-line biologics. Such patients may be more likely to have less TNF-dependent disease, and could benefit from subsequent treatment with a targeted therapy of different class. However, this attractive hypothesis has still not been confirmed by clinical data, and the different biologics, including other TNF inhibitors, seem to work similarly in patients without response to TNF blockers.<sup>9</sup> The network involved in the pathogenesis of RA may be so complex, with many interactions between cells and between cytokines,<sup>10</sup> that targeting different molecules in this network may have a roughly similar effect on the downstream process leading to joint inflammation and destruction. Patient populations with inadequate response to TNF inhibitors are a major challenge for rheumatologists in clinical practice, and future drug developments should focus on therapies for these refractory patients.

The development of biologics that selectively block additional specific cytokines, such as the BAFF-antagonists and GM-CSF antagonists reviewed here, is of considerable theoretical importance, and may yet turn out to very beneficial for certain subsets of patients. For the large populations of patients with RA and other inflammatory arthritides, these developments are more likely to represent rather modest steps forward. True progress beyond cytokine-directed and cell-directed immunomodulators will have to come from better strategies to identify patients earlier, and initiation of the appropriate therapeutic strategies as expeditiously as possible.

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