Biobetters in patients with immune-mediated inflammatory disorders: an International Delphi consensus

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Author’s contribution
LPB and SD conceived the study. FD and VS wrote the manuscript and created tables and figure.
DA, AH, FM, CS, SCN, SAA, EC, HSK, PB, PO, PGK, SG, LPB, and SD critically reviewed the content of the paper. All authors discussed the statements and contributed to the final manuscript.
Abstract

Several efforts have been made to improve the available therapeutic armamentarium of patients with immune-mediated inflammatory disorders (IMIDs) leading to the development of biobetters. To date, there is no commonly accepted definition of biobetters. Sixteen physicians with expertise in the field of IMIDs from eleven countries attended a virtual international consensus meeting to provide for the first time a definition of biobetter and to identify unmet needs on this topic. Improvements in clinical outcomes and drug pharmacology were considered crucial for the definition of biobetters, while safety profile and patient acceptability were not. Clinical studies are required to validate this definition and to investigate the role of biobetters in the management of patients with IMIDs.

Keywords: immune-mediated inflammatory disorders, biobetters, definition, consensus
Introduction

Patent expiration of the first biologics has led to the development of biosimilars defined as drugs that are highly similar to the approved reference product, with negligible differences in terms of efficacy, safety, and tolerability [1–3]. Biosimilars proved to be as effective and safe as the originators, leading to significant cost savings and impacting on healthcare systems resources [4]. Due to technology advances, improved versions of the approved biologics have been developed and the new concept of biobetter has emerged [5]. However, what should be exactly better in these innovative drugs is still an open question [6]. The need for a definition is strengthened by the recent development of a new subcutaneous (SC) formulation of CT-P13, biosimilar of infliximab reference product, that was approved by the European Medicine Agency (EMA) for the treatment of patients with immune-mediated inflammatory disorders (IMIDs), such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, Crohn’s Disease (CD), and ulcerative colitis (UC) [7, 8]. In clinical studies, CT-P13 SC showed to offer clinical advantages in terms of pharmacokinetics, with higher pre-administration serum levels and more stable concentrations compared to the intravenous (IV) formulation [9, 10]. Besides a lack of consensus on nomenclature, uncertainty is also related to the absence of a standardized guidance from major regulatory agencies. In fact, the EMA “hybrid” pathway takes into account applications for “a generic medicine that is based on a reference medicine but has a different strength, a different route of administration, or a slightly different indication from the reference medicine”, relying on data for both the originator and new drugs [11]. On the other hand, Food and Drug Administration (FDA) do not consider biologics differing from approved products under the biosimilar approval pathway and it requires a full biologics license application [12]. It follows that the SC version of CT-P13 was perceived as a new drug by the FDA, requiring pivotal clinical trials in each indication, whereas the EMA followed the “hybrid” pathway in which clinical studies were needed besides those required for biosimilar approval. To date, there are several questions about the use of
biobetters in IMIDs and no validated definition is available. For this reason, we conducted a systematic literature review on biobetters in patients with IMIDs and organized an international expert consensus meeting to provide a reliable definition of biobetters and to identify the unmet needs on this topic.

Methods

A virtual consensus meeting including 11 gastroenterologists (FD, VS, AH, FM, SCN, SAA, PB, PAO, SG, SD, and LPB), 4 rheumatologists (DA, CS, EC, and HSK) and 1 colorectal surgeon (PK) with expertise in the field of IMIDs from eleven countries worldwide (Argentina, Austria, Belgium, Brazil, France, China, Germany, Italy, Portugal, United Arab Emirates, and United Kingdom) was held on January 13, 2021. A systematic literature review was independently conducted by two authors (FD and VS) in the PubMed/MEDLINE, EMBASE, and Web of Science databases up to January 2021 to identify all studies reporting data on biobetters in patients with confirmed IMIDs (Figure 1) (Appendix). The literature evidence was shared and discussed among the participants. Five preliminary consensus statements were drafted by 4 participants (FD, VS, LPB, and SD) and were anonymously voted by all experts using a Delphi consensus methodology through a virtual platform (Supplementary table 1) [13]. Statements were approved if ≥75% of participants agreed. If agreement was not reached, the statement was discussed, rephrased, and re-voted. If no consensus was reached in the second round of votes the statement was removed. New statements could also be formulated during the virtual meeting, discussed, and voted. According to the GRADE system, two authors (FD and VS) independently graded the quality of the evidence supporting each statement and any disagreement was resolved through the opinion of a third author (LPB or SD) [14]. All experts were involved in drafting the manuscript and approved its final version.
**Results**

**Systematic review**

A total of 258 articles were identified through our systematic search (PubMed, 92; Embase, 116; Web of Science, 50). After removing duplicates and reviewing titles and abstracts, 15 studies were evaluated for full-text analysis. Eight studies were excluded as they were not focused in the field of IMIDs. Finally, 7 studies were included in our systematic review [15–21]. Most studies were in vitro studies (6 [86%])[15–20] followed by a phase I clinical trial (14%)[21] (Tables 1). All studies were of low quality according to the Newcastle Ottawa Scale (Table 2). In all studies biobetters were defined as molecules with generic enhanced properties compared to an approved biological drug. Four (57%) studies tested improved versions of anti-CD20 rituximab [17–20], while the remaining focused on biobetters of anti-TNFα drugs (adalimumab in 2 cases [29%] [15, 16], infliximab in one [14%] [21]). Four studies (57%) reported an improved efficacy of the new molecule in vitro (e.g., increased antibody-dependent cell mediated cytotoxicity) [16–18, 20], two [29%] described an enhanced conformational stability [15, 19]. A favorable tolerability profile was considered in one study (14%) [21].

**Statements**

Two preliminary statements were approved in the first voting round. Of the 3 not approved statements, 2 were not approved during the second voting and were removed, while 1 was discussed, reformulated, and approved. Finally, a new statement was proposed, voted, and accepted on the first round of votes, ultimately leading to the approval of 4 statements (Table 3).
Statement 1: Biobetter is a modified version of a specific approved biologic that enhances clinical outcomes (e.g., improved efficacy) and/or drug pharmacology (e.g., pharmacokinetics and/or pharmacodynamics)

The approved definition comes from the common expert opinion that a biobetter is better than an existing drug. The improvement should include a clear superiority over the reference drug in terms of outcomes such as clinical efficacy or pharmacological characteristics. On the other hand, a non-inferior drug should not be considered as a biobetter. A clear example of biobetter is provided by obinutuzumab, an anti-CD20 monoclonal antibody approved for the treatment of patients with chronic lymphocytic leukemia (CLL) or follicular lymphoma (FL) [22, 23]. It was engineered to overcome mechanisms of rituximab resistance as a type II, glycoengineered monoclonal antibody, which takes advantage of the presence of non-fucosylated sugars on the Fc portion in order to generate a more potent effector response in the recipient [24]. Two randomized controlled trials demonstrated the improved efficacy of obinutuzumab as a rituximab biobetter [25, 26]. Obinutuzumab showed to be more effective than rituximab in CLL patients leading to prolonged median progression-free survival (26.7 vs. 11.1 months, hazard ratio [HR] for progression or death = 0.18; 95% confidence interval [CI], 0.13-0.24; p < 0.001) [25]. Similarly, a significantly higher progression-free survival rate was reported in patients with advanced FL treated with obinutuzumab compared with rituximab after a median follow-up of 34.5 months (80% vs. 73.3% respectively, HR = 0.66; 95% CI, 0.51-0.85; p = 0.001) [26].

Moreover, experts agreed on the relevance of improved pharmacology parameters such as trough concentrations in the biobetter definition. This is supported by a phase I trial on CT-P13 including 131 IBD patients [10]. Subjects were randomized at week 6 to CT-P13 SC or CT-P13 IV, after an IV induction. After 30 weeks, patients in the IV arm were switched to either SC 120 or 240 mg according to their body weight [10]. Clinical response rates (defined as a decrease in partial Mayo
score of ≥2 points and rectal bleeding subscore ≤ 1 and in Crohn's Disease Activity Index [CDAI] of ≥70 points) were comparable between the two groups after 30 weeks, but the mean trough serum concentrations were higher in the SC cohorts than in the IV cohort and were persistently above the therapeutic threshold (5 μg/ml) throughout the study visits [10]. Advantages in terms of pharmacokinetics are corroborated by the results of a phase I/III study conducted in RA patients treated with CT-P13 SC [27, 28]. After an IV induction, patients were randomized either to maintain IV formulation or to switch to SC drug at week 6. The mean trough concentrations in the SC arms were higher compared with those of IV cohort and were stable over the target therapeutic level (1 μg/mL) throughout the study period [27]. Interestingly, safety profiles were comparable between SC cohorts and IV cohorts in both IBD and RA studies [10, 27–29].

Recently, a new formulation of vedolizumab SC has also been developed. Preliminary findings from the phase III VISIBLE 1 trial enrolling 216 patients with moderately-to-severely active UC are available [30]. After an IV induction, patients were randomly assigned to SC vedolizumab, IV vedolizumab, or placebo as maintenance therapy at week 6 [30]. The primary endpoint of clinical remission (defined as a total Mayo score of ≤ 2 and no individual subscore >1) at 12 months, was achieved in a significantly higher proportion of patients in the SC and IV vedolizumab groups than in placebo arm (46.2% and 42.6%, vs. 14.3% p < 0.001). SC vedolizumab was also associated with a greater endoscopic improvement at week 52 compared with placebo (p < 0.001). Of note, median trough levels of vedolizumab were higher in the SC than in the IV group (39.8 mg/ml, 90% CI, 20.8–75.4 mg/ml vs. 32.2 mg/ml, 90% CI, 16.5-60.7 mg/ml, respectively) [30]. It should be mentioned that an initial version of this statement included patients’convenience among the improved features of biobetters. Recent studies reported the development of new auto-injector devices for SC administration of biological drugs [31, 32]. In 2 studies, the new devices were preferred over the standard tools (e.g. prefilled syringe) by patients with IMIDs improving patients’ quality of life [31, 32]. Although a normalized health-related quality of life has recently been
included among the long-term treatment targets of IBD patients [33], patients’ convenience alone was not considered a sufficient improvement to define a biobetter. This is explained with the lack of concrete and well-established endpoints measuring patients’ convenience. In fact, patient’s preference and convenience were measured through self-administered questionnaires using heterogeneous and non-validated endpoints such as acceptability, compliance, and satisfaction [31, 32].

**Statement 2: Robust pharmacovigilance program is required to demonstrate the long-term safety of biobetters in patients with immune-mediated inflammatory disorders.**

As for biosimilars, long real-world studies are needed to sustain the switch to biobetters without safety concerns. Over the past 10 years biosimilars showed to be safely used in all their approved indications as their originators [11]. CT-P13 proved to be as safe as infliximab originator in several real-life cohorts after its authorization [34]. Safety of CT-P13 defined as the rate of all adverse events, infusion reactions, and adverse events causing discontinuation was evaluated in a large cohort of 830 IBD patients [34]. The overall safety profile of CT-P13 was not different from what was expected for the originator (serious adverse events occurrence rate = 19%) [34]. Similarly, a 5-year retrospective analysis conducted over 491 patients with RA and AS treated with CT-P13 reported that treatment-emergent adverse events rate was comparable to that of the originator cohorts (approximately 30%) [35]. Finally, a large systematic review including 14,225 IMIDs patients found no significant differences in safety between biosimilars of etanercept, adalimumab, infliximab, and rituximab and their originators supporting their wide use in daily clinical practice [36]. A rigorous pharmacovigilance system is essential to acquire full information about the safety profile of biobetters, detect unknown and uncommon adverse events, monitor their safety, and assess any changes to their risk-benefit ratio [37].
Statement 3: Decision to use the reference product or the biobetters in clinical practice should be based on the balance between clinical outcomes and costs.

IMIDs highly impact on healthcare systems budgets, due to long-term treatment costs and reduction in work-related productivity of patients [38–40]. The introduction of biobetters could hypothetically lead to the achievement of better efficacy outcomes and/or drug pharmacology with a reduction in direct and indirect costs, thus justifying their use in the field of IMIDs. Biobetters could allow to obtain an improved disease control and consequently reduce the proportion of hospitalizations, surgeries, and escalation of medical therapy. As predicted by budget impact models, treatment with biosimilars was associated with significant cost savings [41, 42]. In Denmark, the use of biosimilars led to a significant decrease in the infliximab cost by around 27 million euros in 2015 [43]. Similarly during the 2017/18 financial year, a cost reduction of £99,400,000 was observed in the United Kingdom (UK) after switching RA and IBD patients to infliximab biosimilars [44].

Biobetters’ approval could increase the available therapeutic options and favor price erosion, ultimately increasing the number of patients to be treated. The impact of biobetters on healthcare system resources should be further investigated in the near future. In addition, more data are needed to support the decision to prefer a drug based on the administration route (e.g., SC vs. IV) in patients with IMIDs. Although changes from IV to SC formulations might result in significant economic advantages in terms of hospital resources, direct monetary cost savings, and infrastructural profits, further studies are required to confirm a real clinical / pharmacological improvement with SC drugs and justify their use [45, 46]

Statement 4: The switch to a biobetter should be individualized based on clinical need and/or a shared decision between physicians and patients.
Improved clinical or pharmacological outcomes could motivate the choice of the switch to biobetters. The switch could also be proposed to patients with stable disease remission or to individuals who could benefit from home treatment. All experts agreed on the relevance of treatment individualization based on the clinical needs, after a shared and informed decision-making process between patients and physicians. Adequate patient information and patient's willingness to be switched to a new drug are essential to enhance patient acceptability and compliance with treatment [47]. Even though there is no available evidence regarding the nocebo effect in patients switched to a biobetter, it is likely that skepticism and reluctance towards a new medical product could turn into low acceptance rates and worse clinical outcomes [48]. An effective and clear communication to patients could be a key strategy to prevent the risk of nocebo effect associated with patients’ negative expectations [49, 50]. Moreover, SC biobetters could have a very timely role during the current health emergency due to the new coronavirus disease 2019 (COVID-19) pandemic. In order to reduce nosocomial exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a study from UK selected 163 IBD patients who were stable and infliximab-responders [51]. Subjects were transitioned from IV to self-administered at home SC CT-P13 every 2 weeks. Preliminary results showed that only 3 patients discontinued the treatment due to reasons that were not considered related to the switch (complications of perianal disease in 2 cases and antibody formation in one), whereas the remaining 160 maintained SC therapy without safety and tolerance concerns [51].

**Research gaps**

Data about biobetters in patients with IMIDs are still scarce. Alignment in guidance from regulatory agencies is expected to make biobetters’ development more feasible and less time-consuming. Moreover, cooperation among regulatory authorities, pharmaceutical industries, and scientific
societies is warranted to inform healthcare providers about the biobetter concept. Since confidence and trust in innovative drugs is fundamental for ensuring a judicious use in clinical practice, studies exploring physicians’ awareness and education are necessary. Future research should focus on measurable endpoints of patients’ convenience, clarifying whether this aspect should be included in the definition of biobetter. It is also essential to investigate whether the nocebo effect might be a relevant phenomenon issue for these medications. Long-term studies are expected to evaluate the occurrence of treatment-related adverse events, to confirm the improved efficacy of biobetters compared with the originator drug, and to assess the impact of these drugs on healthcare resources finances.

**Conclusion**

This international expert consensus provides for the first time a definition of biobetter in patients with IMIDs. Although the level of evidence supporting the statements was not high, improvements in terms of efficacy and pharmacology should be present in a molecule considered as a biobetter. On the other hand, improved safety profile and greater patient acceptability were not deemed sufficient to be included in the biobetter definition. The rationale for biobetter development should be driven by efforts to achieve ever deeper disease remission in patients with IMIDs with greater disease control, leading to significant cost savings. Clinical trials on molecules considered biobetters according to this definition are needed to evaluate their impact on the management of patients with IMIDs.
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https://doi.org/10.3389/fphar.2017.00322


<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Study design</th>
<th>Biological drug</th>
<th>Biobetter definition</th>
<th>Outcome</th>
<th>Results</th>
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<tr>
<td>Reslan et al. (2020)[15]</td>
<td>In vitro study</td>
<td>Adalimumab</td>
<td>Advance in antibody engineering technology leading to the development of a multitude of novel, next-generation antibody-derived products</td>
<td>Evaluating the effect of Fab N-linked glycosylations on the aggregation propensity and the conformational stability</td>
<td>The addition of N-glycans in the Fab domain significantly enhanced the conformational stability</td>
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<td>An et al. (2019)[21]</td>
<td>Phase I clinical trial</td>
<td>Infliximab</td>
<td>Antibodies engineered to have improved properties (e.g., optimized glycosylation profiles) or an engineered Fc domain to increase pharmacokinetic properties</td>
<td>Comparing infliximab that is expressed in SP2/0 cells with CMAB008 produced in a CHO-expression system</td>
<td>CMAB008 has a favorable clinical tolerability</td>
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<tr>
<td>Luchese et al. (2018)[16]</td>
<td>In vitro study</td>
<td>Adalimumab</td>
<td>Biosimilar development</td>
<td>Evaluating binding kinetics and functional analysis of an anti-TNFα monoclonal antibody generated from a productive and stable cell line (CHO)</td>
<td>The CHO-derived cell line expressed an anti-TNFα monoclonal antibody capable of neutralizing activity</td>
</tr>
<tr>
<td>Bennett et al. (2017)[17]</td>
<td>In vitro study</td>
<td>Rituximab</td>
<td>Biological drug showing enhanced properties (e.g., stronger ADCC)</td>
<td>Comparing rituximab with an afucosylated antibody glycoform with two terminal galactose residues generated through a plant expression system</td>
<td>The remodelled afucosylated antibody showed similar binding affinity to the CD20 antigen and significantly enhanced ADCC.</td>
</tr>
<tr>
<td>Khoo et al. (2017)[18]</td>
<td>In vitro study</td>
<td>Rituximab</td>
<td>Enhanced versions of biosimilars</td>
<td>Demonstrating that a humanized version of rituximab could be generated using the logical and bioinformatics approach with potential for development into useful treatment and diagnostic tools</td>
<td>This anti-CD20hIgG-A4 demonstrated higher binding affinity and cytotoxic effects compared to rituximab.</td>
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<tr>
<td>Courtois et al. (2015)[18]</td>
<td>In vitro study</td>
<td>Rituximab</td>
<td>Biological drug with enhanced properties such as enhanced efficacy or reduced immunogenicity</td>
<td>Using a computational tool to identify aggregation-prone regions and develop a biobetter with enhanced stability through selected mutations</td>
<td>Two quadruple selected mutations lead to rationally designed biobetters with enhanced rituximab stability.</td>
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<tr>
<td>Li et al. (2013)[20]</td>
<td>In vitro study</td>
<td>Rituximab</td>
<td>Biological drug with genetic enhanced properties</td>
<td>Investigating if the reduction in fucose resulted in a significant improvement in FcγRIIIa binding and antibody-dependent cell-mediated cytotoxicity</td>
<td>The reduction in fucose resulted in a significant improvement in FcγRIIIa binding and ADCC</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADCC: Antibody-Dependent Cell Mediated Cytotoxicity, CHO: Chinese hamster ovary, Fab: fragment antigen binding, FcγRIIIa: Fcγ receptor IIIa
Table 2. Quality of the studies included in the systematic review according to the Newcastle-Ottawa Scale.

<table>
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<th>Study</th>
<th>Item 1</th>
<th>Item 2</th>
<th>Item 3</th>
<th>Item 4</th>
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<th>Item 8</th>
<th>Score</th>
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<td>Reslan [15]</td>
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<td>★</td>
<td>★</td>
<td>★</td>
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<td>An [21]</td>
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<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
<td></td>
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<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<td></td>
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<tr>
<td>Bennett [17]</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td></td>
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<td>Khoo [18]</td>
<td>★</td>
<td>★</td>
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<td>4</td>
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<tr>
<td>Courtois [19]</td>
<td>★</td>
<td>★</td>
<td>★</td>
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<td>4</td>
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<tr>
<td>Li [20]</td>
<td>★</td>
<td>★</td>
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<td>★</td>
<td>★</td>
<td></td>
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<td>4</td>
</tr>
</tbody>
</table>

*Items:* 1, representativeness of the exposed cohort; 2, selection of the non-exposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at start of study; 5, assessment of outcome; 6, follow-up was long enough for outcomes to occur; 7, adequacy of follow-up (>75% follow-up, or description for those lost); 8, comparability of cohorts on the basis of the design or analysis.
| Statement 1 | Biobetter is a modified version of a specific approved biologic that enhances clinical outcomes (e.g. improved efficacy) and/or drug pharmacology (e.g. pharmacokinetics and/or pharmacodynamics).  
(93% acceptance rate, low-quality evidence) |
| Statement 2 | Robust pharmacovigilance program is required to demonstrate the long-term safety of biobetters in patients with immune-mediated inflammatory disorders.  
(100% acceptance rate, low quality evidence) |
| Statement 3 | Decision to use the reference product or the biobetters in clinical practice should be based on the balance between clinical outcomes and costs.  
(100% acceptance rate, low quality evidence) |
| Statement 4 | The switch to a biobetter should be individualized based on clinical need and/or a shared decision between physicians and patients.  
(100% acceptance rate, low quality evidence) |
Supplementary table 1: Preliminary statements

| Statement 1 | Biobetters are improved versions of the approved biologics, which have been modified in order to enhance clinical outcomes (e.g. improved efficacy, safety, or tolerability) or patients’ convenience (e.g. pharmacokinetics parameters, formulation, or administration route). |
| Statement 2 | Biobetter should demonstrate superiority in terms of efficacy, safety, immunogenicity, or patients’ convenience. |
| Statement 3 | Robust pharmacovigilance program is required to demonstrate the long-term safety of biobetters in patients with immune-mediated inflammatory disorders. |
| Statement 4 | The evidence to support the switch from the reference product / biosimilar to the biobetter in daily clinical practice is lacking. |
| Statement 5 | The switch to a biobetter should be individualized based on clinical need and/or a shared decision between physicians and patients. |
Appendix: Methods of the systematic review
Conflict of interest

F D’Amico and V Solitano declare no conflict of interest. D Aletaha received consulting and/or speaking fees from AbbVie, Amgen, Celgene, Gilead, Galapagos, Lilly, Medac, Merck, Novartis, Pfizer, Roche, Sandoz and Sanofi/Genzyme. S Al Awadhi declares no conflict of interest. P Bossuyt has received financial support for research from AbbVie, Amgen, Janssen, Mundipharma, Mylan, and Pfizer; lecture fees from AbbVie, Janssen, Pfizer, and Takeda; advisory board fees from Abbvie, Arena pharmaceuticals, Bristol-Myers Squibb, Hospira, Janssen, Merck, Mundipharma, Pentax Medical, Pfizer, PSI CRO, Roche, Sandoz, and Takeda. S Ghosh declares consulting fees from Pfizer, Janssen, AbbVie, Takeda, Bristol-Myers Squibb, Receptos, Celgene, Gilead, Eli Lilly and Boehringer Ingelheim and speaker fees from AbbVie, Janssen, Takeda, Ferring, Shield, and Falk Pharma; outside of the submitted work. E Choy has received research grants from Bio-Cancer, Biogen, Novartis, Pfizer, Roche, Sanofi and UCB, consultancy from Abbvie, Amgen, Biogen, Biocon, Chugai Pharma, Eli Lilly, Gilead, Janssen, Merck Serono, Novartis, Pfizer, Regeneron, Roche, R-Pharm and Sanofi, speakers fee from Amgen, Bristol Myers Squibb, Chugai Pharma, Eli Lilly, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, and UCB. C Selmi declares no conflict of interest. A Hart reports she has served as consultant, advisory board member, or speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire, and Takeda, and also serves on the Global Steering Committee for Genentech. PG Kotze reports personal fees from Abbvie, Janssen, Pfizer, Novartis, Ferring and Takeda; research grants from Pfizer and Takeda. F Magro has served as a speaker and received honoraria from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratorios Vitoria, Ferring, Hospira, and Biogen. S C Ng reports grants from Ferring and personal fees from Takeda, AbbVie, Janssen, and Tillotts Pharma. PA Olivera received consulting fees from Abbvie, Takeda, and Janssen and lecture fees from Takeda and Janssen. L Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech,
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