Therapeutic innovation in adult-onset Still's disease (and other rare inflammatory disorders): how to secure evidence-based medicine?

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Adult-onset Still's disease (AOSD) is a rare inflammatory disorder with heterogeneous clinical presentation and unspecific features (spiking fever, pharyngitis, arthritis, skin rash with elevated acute phase reactants).[1] Its diagnosis is one of exclusion, and necessitates ruling out many other conditions, notably neoplastic and infectious ones. Based on clinical experience and literature, a 'dichotomous view' of AOSD is emerging, with two distinct AOSD clinical subtypes, potentially requiring distinct treatments[1 2]: a non-Mendelian autoinflammatory disease with pre-eminent systemic symptoms and intense inflammatory state, sometimes associated with life-threatening complications such as reactive haemophagocytic lymphohistiocytosis, and a rheumatic disease with pre-eminent chronic polyarthritis and possibly destructive polyarthritis with lower inflammatory state. Currently, this 'dichotomous view' is not only supported by clinical observations, but also by findings on cytokine profiles and responses to biotherapies in some refractory patients.[2] Indeed, interleukin (IL)-1□, IL-6 and IL-18 would be associated with 'systemic AOSD', whereas tumour necrosis factor alpha (TNF-□), interferon gamma (IFN-□) and IL-8 would be of greater involvement in 'rheumatic AOSD'.[3–6] Of note, this dichotomous approach remains controversial and the choice of biologics (targeting 'appropriate' cytokines) is still empirical in refractory patients. One could hope that cytokine monitoring provides information towards a personalised approach. However, such immunobiological tools are technically difficult to develop for daily practice and remains phantasmagorias even though they would be very useful at the time when several biotherapies are already successfully used or are under evaluation in clinical trials (https://clinicaltrials.gov/).

In *Annals of the Rheumatic Diseases*, Gabay *et al* report the results of a multicentre, open-label study evaluating the safety and efficacy of the recombinant IL-18-binding protein (IL-18BP), tadekinig alfa, in patients with difficult-to-treat AOSD.[7] IL-18 was indeed reported increased in patients with AOSD and systemic onset juvenile idiopathic arthritis. This work provides the first demonstration of the therapeutic benefits obtained with IL-18BP in AOSD. Hence, this study represents a proof-of-concept suggesting that IL-18 inhibition could be a therapeutic option in this systemic inflammatory disease, with a reasonably acceptable safety profile. Actually, the drug appears mildly efficient, in a subgroup of incompletely controlled and moderately severe AOSD. So, at this stage, tadekinig may represent an interesting tool for some patients with AOSD. One could hope that IL-18 blockade would provide greater benefit in a subgroup of patients with systemic form of AOSD rather than articular forms (herein recruited for this study). Thus, further trials are required to establish IL-18BP at its true place within therapeutic armamentarium.

Undoubtedly, the current study suffers from several methodological limitations (including lack of control group, small number of included subjects and unbalanced groups of patients). These limitations are linked both to the open-label, uncontrolled, design of the study and also to the rarity and heterogeneity of AOSD. This is usual in AOSD and should not limit the scientific interest of physicians for new biologics in this condition. Efficacy of anti-IL-1 agents (ie, anakinra[8] and canakinumab[9]) was demonstrated in randomised controlled trials (RCT) in systemic-onset juvenile idiopathic arthritis, which is usually considered as the juvenile equivalent of AOSD. Since then, canakinumab[10–12] and anakinra[13–19] accumulated demonstration of their efficacy in case reports or series on AOSD, but not in RCT. At the end of a chase, both biologics obtained authorisation, which allows more easily their beneficial use for some patients. At this point of discussion, the therapeutic innovation and the great interest exhibited by pharmaceutical industry in this rare disease should be commended. However, rare diseases (such as AOSD) may also be economical niches for industrials, and this represents a risk for trials (and drug development) of being insufficiently relevant to the goals of patient's management.

Medical necessities and economical strategies should not be opposing players and must act together to promote therapeutic innovation, a real challenge, particularly in rare diseases.[20 21] Of course, the development of a new drug requires considering economical standpoints. In this complex interplay, the governing law of clinical trials should be carefully handled since it may represent a double-edged sword for physicians. On the one hand, physicians should be in a position to provide precise and contemporary definitions of both disease and treatment goals, but on the other hand, they should not blindly and suddenly abandon their conception of disease (definitions of the disease, remission, refractory forms and so on) and change their practice without taking a critical distance. An example may be found within another inflammatory disease, giant cell arteritis (GCA). Since decades, physicians are in search of steroid-sparing agents and also new drugs for refractory forms of GCA. Responding to this medical necessity, pharmaceutical industry recently provided new drugs such as tocilizumab, an IL-6 inhibitor.[22] Thus, tocilizumab proved to be effective in reducing vascular inflammation in GCA and should be useful in so many patients. Nevertheless, physicians should not forget the initial goal of therapy in this disease and ask themselves: how have we been managing steroids tapering in GCA since decades? Meeting how many real failures? And which risk for each individual patient? Anti-IL-6 agents may be great molecules, but do they represent a genuine revolution for every patient with GCA or only a subgroup? So, the question would be: which subgroup(s) to target?[23–25] One

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shall keep this perspective in mind when attempting to manage such diseases and before changing practice or the whole paradigm. Generally speaking, we should reconcile medical and economical necessities, in order to benefit from therapeutic innovation without overlooking the lessons from the past.

Indeed, an emerging problem could be a discrepancy between economical standpoints and scientific objectives serving patients' needs. So, the emerging question may become: 'what really drives therapeutic innovation?' The unpredictability and versatility of pharmaceutical industry in the last decades, mentioned by some authors,[26] appears quite disconcerting both for physicians and patients and may contribute to a loss of confidence and eventually a distrust of industrial partners. In this context, the physicians, as well as the health authorities and managers, should be very careful with the results of trials and their applications in everyday practice.

This careful consideration of 'evidence-based medicine' (EBM) is even more complex in AOSD, since recommendations are lacking and merely impossible to establish because of methodological limitations inherent to this rare and heterogeneous disease.[27] In order to summarise the peculiar challenge regarding AOSD, here are some issues: first, the definition of AOSD is vague, since it is not based on definite histopathological demonstration of tissue lesions, and leads to some uncertainty in diagnosis; second, in daily practice, diagnosis is based on criteria,[28 29] which were developed for classification; third, strong biomarkers are not available and even glycosylated ferritin appears a disappointing marker in practice[30]; fourth, prognostic scores (such as Pouchot's 'systemic score') remain to be validated in larger cohorts.[31 32] So, what is the goal of therapy in AOSD and how to define a primary end-point in clinical trials? Since AOSD is very heterogeneous both in presentation and disease course, which subgroup of patients should be targeted? More precisely, we think it is very important to figure out which patients are treated in such trials. This may be quite difficult for readers and reviewers to find this information in the published studies. For instance, is the population made of 'rheumatoid' or 'systemic' AOSD? What is the disease course: first flare? polycyclic or chronic articular disease? These questions are not anecdotal. A third of patients may experience one self-limited disease flare, which may sometimes be easily managed by non-steroidal anti-inflammatory drugs or corticosteroids.[31] So, is it legitimate to develop new approaches for these patients? Should not we focus on refractory patients with AOSD, the one with true unmet medical need? Obviously, all these considerations may affect the relevance of the results obtained from clinical trials and one can easily imagine the hardness to transpose such results into everyday practice.

Anyhow, we physicians have to promote research and innovation. We also have to convince health authorities of the necessity of innovative drugs. Trials are useful and provide demonstration. Considering ethical aspects, we also owe patients to develop innovative strategies to cure the most refractory forms of AOSD. In that sense, IL-18BP may be such an alternative therapeutic option for some patients with difficult-to-treat disease. So, even if the study by Gabay *et al* is not perfect and may appear methodologically controversial, we should be delighted by the development of new effective drugs in AOSD. However, considering the above-mentioned comments, it is very uncertain that the required further studies testing IL-18BP in AOSD will be conducted by industrials. Targeting a subgroup of patients within AOSD niche may not be a good strategy for them. We physicians do not know much about that. Industrials and we stem from very different places, but we are partners, acting for the development of therapies. As already claimed by many others, we should work together while keeping in mind the potential sponsorship bias associated with industrial funded trials. Beyond this common assumption, we could obviously provide something very useful for the relevance of future trials in AOSD, that is, methodological recommendations. Consequently, we should combine efforts at national and international levels to develop independent institutional research in AOSD and better apprehend this multifaceted disease. Only one such advance will allow us to improve the relevance of trials and further secure EBM in this rare entity, and thus refine the use of innovative drugs in everyday practice.

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