Editorial paper

Reumatologia 2021; 59, 6: 353–355
DOI: https://doi.org/10.5114/reum.2021.112348

Interleukin 1 inhibitors in monogenic autoinflammatory diseases – one size does not fit all

Ewa Więsik-Szewczyk

Department of Internal Medicine, Pneumonology, Allergology and Clinical Immunology, Central Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine, Warsaw, Poland

In 1950s, researches supported a hypothesis that the endogenous pyrogen, presumably derived from polymorphonuclear cells, was an essential fever-inducing factor [1]. Later on, it was identified as interleukin 1 (IL-1), also known as lymphocyte activating factor, leucocytic endogenous mediator, catabolin, osteoclast activating factor or hemopoetin 1; probably not to mention all. Cumulated data lead to conclusion that IL-1 is a key mediator of host responses to a microbial invasion, that IL-1 represents a true substance produced during an infection and inflammation, and that its biologic activities account for several aspects of the acute-phase reaction [2].

Currently the term IL-1 covers two cytokines – IL-1α and IL-1β which are encoded by 2 separate genes, and play crucial role in the acute and chronic inflammatory process. It is not surprising that the therapeutic inhibition of IL-1 pathway has been attempted in many chronic autoimmune and inflammatory conditions. However the results of the studies of IL-1 blockers in RA conducted almost 25 years ago showed only a modest effect of the IL-1 blockade, especially in comparison with highly effective TNF inhibitors.

By contrast to autoimmune diseases the use of IL-1 blockers was found to be strikingly effective and beneficial in autoinflammatory diseases (AIDs). The first definition for AIDs was proposed in 1999 [3]. It was based mainly on two diseases whose related genes had then been identified: familial Mediterranean fever (FMF) and factor receptor-associated periodic syndrome (TRAPS). Since this first proposal, the field of recognized monogenic autoinflammatory syndromes has expanded and the definition has evolved. According to the latest, although probably not yet final, consensus, AIDs are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants) and the lack of the primary pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production) [4].

The prototypic monogenic autoinflammatory conditions are grouped as inflamasomopaties and are associated with excessive IL-1 signaling. The group covers: cryopyrin-associated periodic fever syndrome (CAPS), TRAPS, mevalonate kinase deficiency/hyper IgD syndrome and FMF. Since the initial description of its efficacy in 2003 [5] the position of IL-1 blockers in CAPS has been confirmed by clinical experience and randomized clinical trials. Il-1 blockers received a strong recommendation as a first-line treatment in CAPS [6]. Later on, the strategy was also supported in 3 other inflamasomopaties [7].

Two IL-1 inhibitors have been registered and are used with success in Europe, having presented excellent long-term effectiveness in terms of drug retention rate in real life [8].

Anakinra is a recombinant non-glycosylated form of the human IL-1 receptor antagonist that binds to IL-1 receptor type I and acts as a competitive inhibitor with IL-1α and IL-1β in a way that mimics the activity of the endogenous IL-1R antagonist. The recommended initial dose of anakinra is 100 mg/day subcutaneously in adults and 0.5–2 mg/kg per day in children, who may require an increased dosage up to 5–8 mg/kg per day to maintain a remission.

Canakinumab is a fully humanized IgG1 monoclonal antibody which neutralizes IL-1β. Given its long half-life of 26 days, canakinumab administration is recommended subcutaneously at 2–4 mg/kg in children and at a minimal dose of 150 mg in adults, every 4–8 weeks in both age groups. Both canakinumab and anakinra had the favorable safety profile supported by the "real life" evidence [9]. The most frequent adverse event by far of anakinra is the injection site skin reaction, which is reported in up to 70% of patients. In clinical practice.

Address for correspondence:
Ewa Więsik-Szewczyk, Department of Internal Medicine, Pneumonology, Allergology and Clinical Immunology, Central Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine, 128 Szaserów St., 04-141 Warsaw, Poland, e-mail: ewa.w.szewczyk@gmail.com
Submitted: 14.12.2021; Accepted: 16.12.2021

these local reactions decline over time without the need to discontinue the treatment.

Until 2017, Polish patients did not have access to the reimbursed treatment with IL-1 blockers. The breakthrough came in October 2017 with the launch of the Congenital Autoinflammatory Syndromes Treatment Programme, reimbursed by the Ministry of Health and coordinated by the Autoinflammatory Diseases Section of the Rare Diseases Team [10]. The indications were updated in 2020, and anakinra is currently reimbursed for use in IL-1-mediated autoinflammatory syndromes. In the first year of the programme initiation, 24 patients were enrolled. Up to the end of 2021, over 75 patients, mostly with monogenic AIDs, received anakinra and more new patients are expected [10]. Canakinumab is still not reimbursed in Poland.

Despite a great progress in understanding and treatment of AIDs, many doubts and problems have to be addressed. Monogenic AIDs remain life-long conditions which strongly impact the patient's life and – untreated – lead to an irreversible damage, disability and premature death. Given that, the care and treatment have to be carried lifelong and should be suited to patient's needs in order to minimize the treatment burden [11]. Although there are two IL-1 blockers available in Europe, the recommendation which drug should be the first line is missing. There are no strict medical indices available to support the choice.

In addition, there are no clear recommendations for dose adjustment decisions. Patients with more severe phenotypes may require an early dose escalation to induce a remission. In contrast, patients with a milder disease or on a long-term remission might be eligible for a dose reduction especially during the maintenance phase. Still, the activity and severity indices validated in purpose to monitor patients in real life rather than in clinical trials, are lacking. The clear cut-off values of the biologic inflammation is not strictly defined to support therapeutic decisions – some authors claim any increase in acute phase reactants to be a guide, others recommend CRP or SAA values above 10, 25, 30 mg/l. We do not know if a persistent biological inflammation without clinical symptoms is a specific indication for the dose increase, especially if it means twice a day injections of anakinra for an adult patient who feels completely well.

In real life, on-demand treatment with anakinra is ordered at the signs of disease flare, but long term data assessing formally this regimen is lacking [11]. And last but not least, we do not have any clues about when and whether systematic treatment can be suspended and watch-and-wait strategy introduced.

In cryopyrin-associated periodic fever syndrome, there is no evidence for efficacy of any other therapy except IL-1 blockage. From this point of view, therapeutic options limited just to 2 medications seem to be fearfully limited. Definitely, there is a need to search novel therapeutic options which could be alternative to biologic Il-1 inhibitors. Hopefully new, oral, selective inhibitors of the NLRP3 inflammasome, tranilast, inzomelid and dapansutrile are under way [12].

Finally, I would like to mention one practical point which touches the diagnosis of monogenic AIDs. As all that glitters is not gold, only a minority of recurrent fevers is caused by monogenic AIDs which are ultrarare condition. And last but not least, not all monogenic AIDs are driven mainly by excessive IL-1 signaling, even if they share clinical features with classical inflamasomopaties. NLRC4 related AID is an example and a case when IL-18 blockade instead of IL-1 inhibition is more beneficial. VEXAS syndrome, SAVI or ADA2 deficiency are other examples of monogenic AIDs which are refractory to IL-1 inhibition.

To conclude anakinra and canakinumab are targeted, effective treatments in inflamasomopaties caused by an excessive activation of IL-1 pathway. However the specific treatment adjustment, dosing and monitoring frequency should be tailored to each patient.

The author received educational fee from Sobi, ad board and lecture fee from Novartis.

References

1. King MK, Wood WB. Studies on the pathogenesis of fever. J Exp Med 1958; 107: 291–303, DOI: 10.1084/jem.107.2.291.
2. Dinarello CA. Interleukin-1. Rev Infect Dis 1984; 6: 51–95, DOI:10.1093/clinids/6.1.51.
3. McDermott MF, Aksentijevich I, Galon J, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999; 97: 133–144, DOI: 10.1016/s0092-8674(00)80721-7.
4. Ben-Chetrit E, Gattorno M, Gul A, et al. Consensus proposal for taxonomy and definition of the autoinflammatory diseases (AIDs): a Delphi study. Ann Rheum Dis 2018; 77: 1558–1565, DOI: 10.1136/annrheumdis-2017-212515.
5. Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med 2003; 348: 2583–2584, DOI: 10.1056/NEJM200306193482523.
6. ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis 2015; 74: 1636–1644, DOI: 10.1136/annrheumdis-2015-207546.
7. Soriano A, Soriano M, Espinosa G, et al. Current Therapeutic Options for the Main Monogenic Autoinflammatory Diseases and PFAPA Syndrome: Evidence-Based Approach and Proposal of a Practical Guide. Front Immunol 2020; 11: 865, DOI: 10.3389/fimmu.2020.00865.

8. Sota J, Rigante D, Cimaz R, et al. Drug survival of anakinra and canakinumab in monogenic autoinflammatory diseases: observational study from the International AIDA Registry. Rheumatology (Oxford) 2021; 60: 5705–5712, DOI: 10.1093/rheumatology/keab419.
9. Malcova H, Strizova Z, Milota T, et al. IL-1 Inhibitors in the Treatment of Monogenic Periodic Fever Syndromes: From the Past to the Future Perspectives. Front Immunol 2021; 11: 619257, DOI: 10.3389/fimmu.2020.619257..
10. Wolska-Kusnierz B, Więsik-Szewczyk E. Recognition and treatment of autoinflammatory diseases in Poland – where are we in 2021? JHPOR 2021;2: 1–9, DOI: 10.7365/JHPOR.2021.2.5.
11. Hentgen V, Koné-Paut I, Belot A, et al. Long-Term Follow-Up and Optimization of Interleukin-1 Inhibitors in the Management of Monogenic Autoinflammatory Diseases: Real-Life Data from the JIR Cohort. Front Pharmacol 2021; 11: 568865, DOI: 10.3389/fphar.2020.568865.
12. Immunome Project Consortium for Autoinflammatory Disorders (ImmunAID), Caseley EA, Poulter JA, Rodrigues F, McDermott MF. Inflammasome inhibition under physiological and pharmacological conditions. Genes Immun 2020; 21: 211–223, DOI: 10.1038/s41435-020-0104-x.