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Commentary

Conflict between efficacy and economy in rheumatoid arthritis treatment: Iguratimod is found at a compromise

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In the last 20 years, while methotrexate (MTX) has become an anchor drug and molecular-targeted drugs such as biologics and Janus kinase (JAK) inhibitors have been introduced, rheumatoid arthritis has become a controllable disease. As a result, clinical remission to prevent joint destruction became the primary therapeutic goal. However, in clinical practice, this remission is achieved for at most 50% of patients. Many clinicians are suffering from a dilemma in that they can't use even if they want to use such effective drugs as biologics or JAK inhibitors. For any disease, three factors should be considered in the actual treatment strategy: the first is the disease factor (e.g., treatment resistance and complications), the second is the patient factor (e.g., non-illness elements: deterioration of physical and cognitive function due to old age, economic basis), and the third is the treatment factor (e.g., options depending on efficacy, dosage forms and costs). A realistic and reasonable care outcome could be found where the three factors are well-balanced. Although biologics and JAK inhibitors are highly effective and support the third treatment factor, their immunosuppressive effects make it difficult to manage infections and thereby conflict the first disease factor. Moreover, since they are expensive and dependent on the patient's financial base, they are against the second patient factor. The three factors are related to each other. Many doctors think that it is better to have more options for the third treatment factor according to various factors in the first and the second ones. In other words, there is a niche of inexpensive drugs that are reasonably effective and relatively safe, even if they are not so effective as molecular-targeted drugs.

Iguratimod is one of those drugs filling that niche. It is a low-cost drug classified as a conventional synthetic type of disease-modifying anti-rheumatic drug (DMARD). Its development began in 1989 when Toyama Chemical Co., Ltd. in Japan discovered a new non-steroidal anti-inflammatory drug (NSAID) with a novel mechanism of action [12]. Reportedly, igratimod suppresses tumor necrosis factor-alpha-induced production of interleukin (IL)-6, IL-8, and monocyte chemoattractant protein via inhibition of nuclear kappa B activation [3]. From the initial phase II trial, its development was promoted as a DMARD named T-614 in collaboration with Eisai Co., Ltd. in Japan. Iguratimod took a long time to be approved in Japan, and it was first approved in China in August 2011, and finally approved in Japan in June 2012.

The phase-III controlled trial from 1999 to 2002 demonstrated superiority of iguratimod to placebo and its non-inferiority to salazosulfapyridine in the rate of 20% improvement in American College of Rheumatology criteria (ACR20) (24 weeks, $n = 376$) [4], and the phase-III placebo-controlled MTX combination trial from 2009 to 2011 also did its superiority to placebo in ACR20 (28 weeks, $n = 253$) [5]. These clinical trials were small-scale, albeit multicenter, and were conducted only in Japan. Subsequent reports were post-marketing surveillance conducted only in Japan (52 weeks, $n = 2666$ in safety and $n = 1614$ in efficacy studies) [6].

This time, Zhanguo Li and colleagues made the first report on the results of a large-scale real world clinical study in China outside Japan [7]. Although it is a single arm, 1759 patients from 48 specialized facilities participated and the efficacy and safety were reconfirmed. Although they did not particularly emphasize, it is noteworthy that they showed the improvement of Hospital Anxiety and Depression Scale (HADS), which is one of the important tools for patient reported outcome (PRO), as efficacy of iguratimod for the first time. Clinical research about labor productivity is expected in the future.

Currently, iguratimod has limited use in the western Pacific region, but it is expected to be introduced and used worldwide as an economical and promising treatment option and to bring welfare to more patients with rheumatoid arthritis.

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Declaration of Interests

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